Imaging of Coronary Atherosclerosis With Multi-Slice Computed Tomography

Gabija Pundziūtė

The studies described in this thesis were performed at the Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands.

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To my family

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Introduction

Chapter 1

Advances in the Noninvasive Evaluation of Coronary Artery Disease With Multislice Computed Tomography

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Abstract

Current non-invasive detection of coronary artery disease (CAD) is based on demonstration of ischemia using stress-rest imaging: this is an indirect way of identifying CAD by demonstration of the hemodynamic consequences rather than direct visualization of the obstructive lesions in the coronary arteries. Multi-slice computed tomography (MSCT) has recently emerged as an extremely rapidly developing non-invasive imaging modality, which allows anatomical imaging of the coronary arteries, or non-invasive coronary angiography. In addition, total plaque burden, plaque morphology and (to some extent) plaque constitution can be assessed by MSCT. The technique also provides information on resting left ventricular systolic function, and possibly resting perfusion. Ideally, stress function and perfusion should also be evaluated, since this would allow detection of ischemia and would complete the picture on CAD. However, this is not routinely performed, since sequential acquisitions are associated with high radiation doses and thus pose a limitation for cardiovascular applications of MSCT. It is anticipated that, with reduction in radiation, MSCT may become an important player in the diagnostic and prognostic workup of patients with known or suspected CAD.

Introduction

Despite worldwide efforts to control cardiovascular risk factors, coronary artery disease (CAD) remains the leading cause of death in Europe and in the USA. The prevalence of CAD in American Caucasians is 5.9%; it is estimated that 700 000 Americans will present with a new coronary event and approximately 500 000 will have a recurrent event in 2006. As a result, CAD is a leading cause of death in the USA with an estimated annual cost of $142.5 billion.[1] The presence of CAD can be non-invasively assessed by demonstrating the presence of myocardial ischemia as myocardial wall motion and/or perfusion abnormalities. Accordingly, indirect information about the presence of CAD is obtained by non-invasive functional imaging techniques. The currently available modalities include nuclear imaging, echocardiography as well as magnetic resonance imaging (MRI). When the above tests are inconclusive or show the presence of ischemia, direct visualization of the coronary arteries with invasive coronary angiography, the current gold standard to diagnose CAD, is performed in order to visualize coronary stenoses, which will further guide therapeutic options. However, in up to 40% of patients with suspected CAD, invasive coronary angiography demonstrates no significant stenoses, thus serves only for diagnostic purposes and is not followed by revascularization. Ideally, invasive coronary angiography, which is associated with patient discomfort as well as a small risk of complications, would have been avoided in these patients. Accordingly, during the past years, extensive efforts have been made in search and development of alternative non-invasive anatomical imaging modalities of CAD, which focus on direct evaluation of coronary stenoses and in certain patient populations could replace invasive conventional coronary angiography. Among these, electron beam computed tomography (EBCT), multi-slice computed tomography (MSCT) and MRI have been developed and have shown promising diagnostic accuracy to detect CAD. Furthermore, the above tests (MRI and MSCT) can (potentially) provide information on multiple aspects of CAD, such as myocardial perfusion and left ventricular systolic function. Concerning left ventricular systolic function, MSCT has the advantage that this information may be derived retrospectively from the same scan performed for coronary angiography, whereas additional acquisitions are required with MRI. Having been introduced in the late 1990s, MSCT is the most recent non-invasive cardiac imaging modality. The technique allows 4D imaging of the entire heart during a single breath hold. Its relatively simple and fast image acquisition protocol has not surprisingly attracted enormous interest and the technique is considered to be at present the most robust modality for non-invasive coronary imaging. An objective of this review is to provide a summary of current status and applications of MSCT with emphasis on the diagnostic evaluation of patients with known or suspected CAD.

Non-invasive Functional Imaging of CAD

Functional imaging for the detection of CAD is based on evaluation of hemodynamic consequences of CAD (i.e. ischemia), rather than direct visualization of coronary arteries. These techniques rely on assessment of perfusion and systolic left ventricular (LV) function during stress and at rest; resting perfusion defects and/or systolic wall motion abnormalities in general indicate myocardial damage (scar formation), whereas stress-induced abnormalities indicate the presence of ischemia. Many contemporary non-invasive imaging modalities are able to demonstrate these changes indicating myocardial ischemia, including single photon emission computed tomography (SPECT), stress (contrast) echocardiography and magnetic resonance imaging (MRI). Two types of stress are used, namely exercise and pharmacological stress, the latter mostly being used in patients who are unable to exercise. A summary of the diagnostic accuracies of these functional imaging modalities to detect CAD is presented in Figure 1.

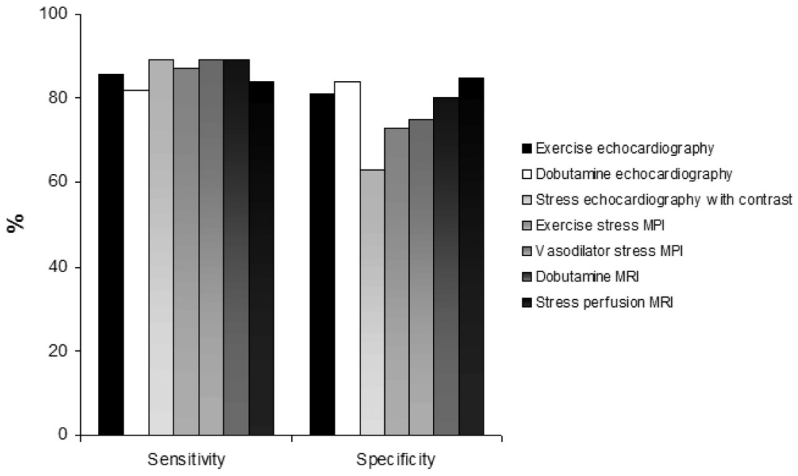

Figure 1. Diagnostic accuracies of functional non-invasive imaging modalities to detect coronary artery disease (data are based on ref. [55-60])

MPI, myocardial perfusion imaging; MRI, magnetic resonance imaging.

Non-invasive Anatomical imaging of CAD

Despite the fact that functional techniques allow reliable evaluation of the presence and extent of CAD, direct evaluation of coronary anatomy is still needed in a considerable number of patients. Thus, the ultimate goal for anatomical non-invasive imaging of CAD is to directly visualize the coronary arteries, although the small vessel size, tortuous course of the arteries and fast motion during the cardiac cycle pose significant challenges. A summary of diagnostic accuracies of non-invasive imaging modalities to detect CAD is provided in Table 1.

Table 1. Diagnostic accuracy of anatomical non-invasive imaging to detect coronary artery disease

Test	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Non-evaluable segments, %	Ref.
EBCT native coronary arteries	87	91			16	1
MRI native coronary arteries	72	87	65	90	17	5
4-slice MSCT native coronary arteries	80	94	67	97	12	5
16-slice MSCT native coronary arteries	88	96	81	98	4	5
64-slice MSCT native coronary arteries	90*	96*	75*	99*	4**	12-17
4-slice MSCT coronary artery bypass graft occlusion	93	96	89	98		21
16-slice MSCT coronary artery bypass graft occlusion	99	98	94	100		21

* Weighted mean is based on ref. [13-17]

** Weighted mean is based on ref. [12-17]

EBCT, electron beam computed tomography; MRI, magnetic resonance imaging; MSCT, multi-slice computed tomography; NPV, negative predictive value; PPV, positive predictive value.

EBCT

EBCT has been developed specifically for cardiac imaging and has been available since the early 1990s. Since its design does not require mechanical movement of an X-ray gantry, data are acquired with a very high temporal resolution (50-100 ms). As can be derived from Table 1, the technique has been proved to be accurate for detection of significant coronary stenoses with sensitivities ranging between 74 to 92% and specificities being in the range of 79 to100%.[2] However, despite the high temporal resolution, the percentage of non-evaluable segments is relatively high (7 to 25%).[2] This is

mostly due to motion artefacts, which may result from data acquisition with prospective triggering in mid-diastolic phase (80% of R-R interval) of the cardiac cycle, not taking into consideration a heart rate of an individual patient. This shortage may be partially overcome by triggering in the end-systolic phase after an increasingly shorter time interval after the previous R wave as heart rate increases. A recent study has demonstrated that with the application of the above protocol, sensitivity increases up to 91%, as compared to 69% as conventional protocol of triggering at mid-diastolic phase is used, and number of non-evaluable segments decreases from 35% to 9%, respectively.[3] Another reason of high percentage of non-enaluable segments is low spatial resolution (1.5 or 3.0 mm) and that the technique requires breath-hold of 30 to 40 s to cover the entire heart.

MRI

The first results on non-invasive coronary imaging with MRI technique were reported by Manning et al in 1993, who observed a sensitivity and specificity for breath-hold 2D MRI of 90% and 92% as compared to conventional coronary angiography.[4] Despite the substantial progress of technical acquisition protocols, such as navigator techniques, however, reported sensitivities and specificities in detecting CAD still show a wide variation, and a considerable percentage of segments suffer from degraded image quality. Currently, the performance of MSCT coronary angiography is better than of coronary MRI, as also recently indicated by Kefer et al, who performed a head-to-head comparison of 1.5 Tesla navigator gated MRI and 16-slice MSCT to invasive coronary angiography. Qualitative analysis of MRI and MSCT images showed sensitivity of 75% and 82% and specificity of 77% and 79%, respectively (p=NS). However, quantitative analysis showed improvement of diagnostic accuracy of MSCT, but not of MRI.[5] It is expected that higher field magnets of 3 Tesla may contribute to improved diagnostic accuracies in the near future.

MSCT

In the late 1990s, MSCT systems were introduced allowing the acquisition of multiple slices instead of 1 slice in a single gantry rotation. As a result, visualization of coronary arteries with this technique had become possible. The latest generations of 16- and 64-slice MSCT scanners have improved spatial and temporal resolution and reduced image acquisition time, which has resulted in significant improvement of image quality and diagnostic accuracy to detect CAD.

Non-invasive imaging of coronary arteries with MSCT
Image acquisition, reconstruction and post-processing

Over the past decade MSCT technology has evolved enormously, resulting in the development of 4-, 16- and 64- and in the near future 256-slice MSCT scanner generations. The most important improvements in the new scanner generations are faster tube rotation speed and better z-axis spatial resolution. A recently introduced development is a dual-source computed tomography (DSCT) system with two X-ray tubes and two corresponding detectors (64-slice), allowing data acquisition during one-quarter of gantry rotation resulting in temporal resolution of 83 ms or as low as 42 ms when multi-segmental reconstruction algorithm is used independent of the heart rate.[6] The first experience with 14 patients examined with DSCT without additional administration of β-blockers showed that 98% of coronary segments could be visualized unimpaired by motion artefacts.[7]

In order to avoid cardiac and breathing motion artefacts, the prerequisites of cardiac MSCT examination are regular heart rate and the ability to hold breath. A heart rate of < 65 beats per minute which can be achieved spontaneously or with the use of β-blockers is desirable for optimal image quality. The average breath hold time for 4-, 16- and 64-slice MSCT is 30 - 40 s, 20 s and 10 s, respectively. The examination of CAD begins with scanning without contrast material injection for evaluation of coronary calcium burden. Prospectively ECG-triggered or retrospectively ECG-gated spiral scanning is performed for evaluation of coronary calcium. The latter provides shorter breath hold times and has less inter-examination variability. However, an important drawback of such protocol is the higher radiation dose. For evaluation of coronary artery stenoses and plaques, the scan is performed with intravenous administration of contrast material which has to be carefully tailored either using a test bolus or automatic bolus triggering technique. Since scan times for imaging of the heart on 4-, 16- and 64-slice MSCT scanners range from 10 to 40 s, 80-140 ml of iodinated contrast with the injection rates of 4-5 ml/s is needed to maintain homogeneous vascular opacification throughout the scan. Saline chasing has proven helpful for avoiding streak artefacts arising from dense contrast material in the superior vena cava and the right atrium as well as for reduction of the volume of contrast medium needed for consistently high vascular enhancement. In contrast no data currently support improved attenuation using multi-phasic over mono-phasic contrast protocols.[8] A helical retrospectively reconstructed scan is performed for evaluation of coronary stenoses. The recent 64-slice MSCT scanners allow acquisition of nearly isotropic voxels with the z-plane resolution of 0.3-0.4 mm as compared to 0.5-0.6 mm with the previous 16-slice

MSCT and >1 mm with 4-slice MSCT. The shortest tube rotation time of 64-slice scanners is 330 ms, resulting in effective temporal resolution of 165 ms and maximal temporal resolution of 83 ms, as compared to 375 ms, 188 ms and 94 ms, respectively with the previous 16-slice MSCT scanner generation.[9] With recent introduction of DSCT scanners, a temporal resolution of 83 ms can be achieved as a single R-R interval is used for image reconstruction or as low as 42 ms when using a segmented reconstruction algorithm that combines data from two cardiac cycles.[7]

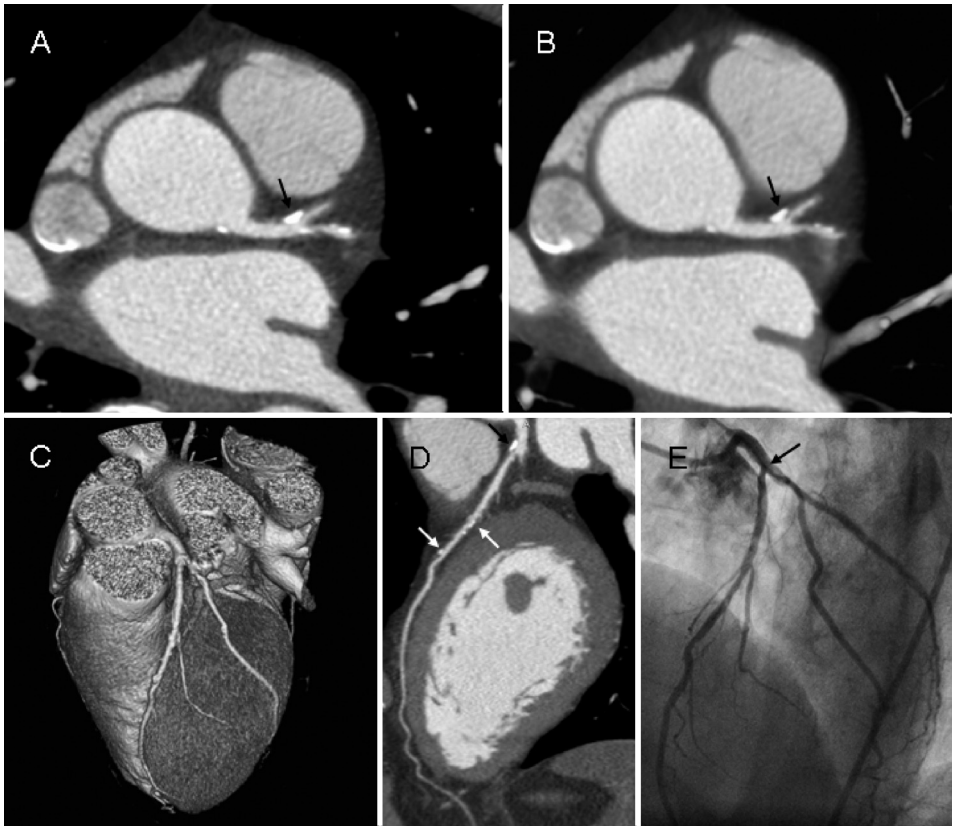

Figure 2. Evaluation of coronary plaques with different post-processing techniques. (A) Axial slice of 0.5 mm thickness is depicted. (B) MIP of 8 mm thickness allows better volumetric evaluation of coronary vessel. (C) 3D volume rendering of the heart. A cMPR is allows the whole course of the coronary artery to be depicted in 2D plane (D). Multiple mixed plaques of LAD are seen in all available reconstructions (white and black arrows). A borderline significant stenosis is seen in the proximal LAD (black arrows), which was confirmed with conventional coronary angiography (E).

LAD, left anterior descending coronary artery; MIP, maximum intensity projection; cMPR, curved multiplanar reconstruction.

Several image post-processing techniques are available to allow clinically useful information to be extracted from several hundreds of individual axial images generated during single MSCT examination.[9,10] The evaluation often begins with the scrolling through axial images, which are considered to be the source images for image post-processing. Multiplanar reconstructions are generated from the volume data set reconstructed from axial images in several arbitrary imaging planes with all available data being represented in the images. Depending on the vascular tissue densities encountered by each ray in the 3D volume, maximum intensity projection reconstructions of various thicknesses may be performed. Volume rendering reconstructions are used to obtain an anatomical overview of the heart and the coronary arteries. Examples of images performed with the available post-processing techniques are provided in Figure 2.

Examination of native coronary arteries

Although diagnostic accuracy to detect significant coronary artery stenoses with the first 4-slice MSCT generation was promising, still 20% of coronary segments had to be excluded from analysis due to non-diagnostic quality.[11] Substantial improvement was achieved by the introduction of 16-slice scanners with submillimeter collimation as well as faster tube rotation times. The sensitivities ranged between 70 to 98%, whereas the specificities varied between 93 to 98%, with on average only 4% (ranging between 0% to 17%) of coronary segments being excluded as non-evaluable.[11] With the introduction of 64-slice MSCT systems, further substantial improvement in image quality has been observed. Examples of coronary angiography with 64-slice MSCT are shown in Figure 2. Currently available data using 64-slice MSCT in comparison to invasive coronary angiography demonstrate sensitivities of 93 to 99% and specificities of 95 to 97% to detect significant coronary stenoses on segment based analysis (Table 2) and 96 to 100% and 90 to 92% on patient based analysis.[12-15] When quantitative analysis is employed, the sensitivity decreases, being 81 and 86%.[16,17] While in some studies all available coronary segments could be included in the analysis,[12,13,15] others have reported exclusion of still 3 to 12% of segments.[14,16,17] In general, the specificity and negative predictive value of MSCT is extremely high and the likelihood of significant CAD if no abnormalities are demonstrated on MSCT is extremely low. Accordingly, the technique may be particularly suitable to exclude CAD and as a result substantially decrease the number of diagnostic catheterizations.

Table 2. Diagnostic accuracy of 64-slice MSCT

Author	Sensitivity, % (no. of segments)	Specificity, % (no. of segments)	PPV, % (no. of segments)	NPV, % (no. of segments)	Evaluable, % (no. of segments)
Leschka et al [13]	94 (165/176)	97 (805/829)	87 (165/189)	99 (805/816)	100 (1005/1005)
Mollet et al [12]	99*	95*	76*	100*	100 (725/725)
Ropers et al [14]	93 (39/42)	97 (1010/1041)	56 (39/70)	100 (1010/1013)	96 (1083/1128)
Pugliese et al [15]	99 (66/67)	96 (408/427)	78 (66/85)	99 (408/409)	100 (494/494)
Raff et al** [16]	86 (79/92)	95 (802/843)	66 (79/120)	98 (802/815)	88 (935/1065)
Leber et al** [17]	81 (59/75)	97 (700/723)	72 (59/82)	98 (700/716)	97 (798/825)

* not specified.

** diagnostic accuracies are based on quantitative evaluation of coronary stenoses with MSCT coronary angiography.

MSCT, multi-slice computed tomography; NPV, negative predictive value; PPV, positive predictive value.

Examination of coronary artery bypass grafts

In patients after bypass surgery, graft occlusion remains a clinically relevant problem as occlusion may occur in up to 15% of venous grafts within a year.[19] In contrast, patency rates are much higher for arterial grafts with occlusion of 5% to 15% of grafts after 10 years.[20] Accordingly, examination of patients with recurrent chest pain complaints after coronary artery bypass graft surgery is another possible application of MSCT. As recently shown in a meta-analysis of the available literature, graft occlusion can reliably be assessed with MSCT.[21] An increasingly better diagnostic accuracy has been shown with the new scanner generations both, to detect coronary bypass graft occlusion and to assess bypass graft stenoses. A pooled analysis of 12 studies where 441 patients with 1246 grafts examined with 4-slice MSCT were included showed overall sensitivity to detect bypass occlusion of 93% and specificity of 96%. Two studies with 144 patients and 416 grafts examined with 16-slice MSCT showed even better sensitivity and specificity of 99% and 98%, respectively.[21] However, observed ability of the technique to detect bypass graft stenosis was lower and the sensitivity was demonstrated to be 70 to 85% with 4- and 16-slice MSCT, respectively.[20] Also, limited data are available on the diagnostic accuracy to detect CAD in the native coronary arteries after coronary artery bypass surgery. This is an important issue, since CAD in the native coronary arteries is more advanced and extensive coronary calcifications are present. Another limitation of coronary bypass graft imaging is the use of metal clips, which potentially cause metal artefacts and hamper evaluation of bypass graft lumen. Currently, no data are yet available on the diagnostic accuracy to detect coronary

artery bypass graft patency with 64-slice MSCT.

Another potential application of MSCT coronary angiography is the evaluation of anatomical information of native vessels and the arterial conduits prior to minimally invasive coronary artery bypass surgery, such as the precise localization of the course of left anterior descending coronary artery, internal mammary arteries and left subclavian artery.[22]

Examination of coronary stents

Despite substantial improvements in interventional revascularization of coronary arteries, the rate of in-stent restenosis remains in the range of >20% in routine clinical practice.[23] Patients presenting with complaints suggestive of in-stent restenosis may accordingly be another subgroup which could benefit from non-invasive imaging of the coronary arteries with MSCT. Coronary stent patency has been extensively evaluated with previous MSCT scanner generations. Four-slice MSCT failed to allow stent lumen assessment regardless of stent type and diameter and the patency of stent was assessed mainly by evaluating the presence of contrast filling in the segment distal to stent.[24] With the introduction of 16-slice MSCT with superior temporal and spatial resolution, the visualization of stent lumen became possible, with 65 to 77% of stents being regarded as evaluable.[25,26] However, stents with larger diameter (>3 mm) were more often regarded as evaluable and rendered higher diagnostic accuracy to detect in-stent restenosis, smaller stents with thicker struts being the main reason for excluding stents from analysis.[25,26] In a study with 40-slice MSCT, a superior diagnostic accuracy to detect in-stent restenosis was observed, as compared to 16-slice MSCT.[27] Only 4.5% of stents were excluded as not evaluable. All except one stent with non-significant in-stent restenosis on MSCT were confirmed with invasive angiography. The sensitivity and specificity to detect restenosis of ≥50% were 63.6% and 87.6%, respectively, with a particularly high negative predictive value of 90.7%. Similar results were observed in a phantom study evaluating the feasibility of stent assessment with 64-slice MSCT, where it has demonstrated that artificial lumen reduction was significantly less with 64-slice than with 16-slice CT, and average visible

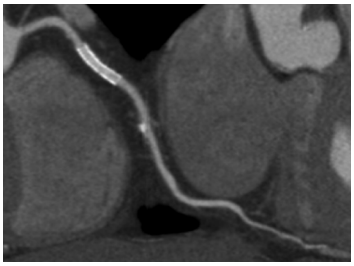

Figure 3. Curved MPR of coronary stent, placed in the right coronary artery. No in-stent restenosis is observed. MPR, multiplanar reconstruction.

stent lumen was 53.4% and 47.5%, respectively.[28] However, a relevant part of the stent lumen is still regarded as not assessable with 64-slice MSCT and the evaluation of subtle neo-intima hyperplasia therefore remains unlikely at least in the near future. In Figure 3, a patent coronary stent imaged with 64-slice MSCT is depicted.

Examination of coronary atherosclerosis: coronary artery calcium scoring

The evaluation of coronary calcium burden is possible using EBCT and MSCT, both providing similar measures.[29] The most widely applicable technique of evaluating coronary calcium burden is the determination of Agatston score.[30] However, it has been shown that volume and mass indexes are superior to traditional calcium score for comparing the results of EBCT and MSCT.[31] Although coronary calcium scoring provides an indication of the extent of atherosclerosis, it does not resemble the total coronary plaque burden, as it identifies only calcified atherosclerotic lesions. Nonetheless, it has been shown that the likelihood of having obstructive CAD increases in parallel with the coronary artery calcium score.[32] Still, coronary artery calcium is not site-specific meaning that calcified segments are not necessarily significantly obstructed and vice versa.[33]

Coronary artery calcium score assessed by EBCT has been studied extensively for risk stratification in asymptomatic patients, and a calcium score <100 has been associated with excellent outcome, with an increase in event rate paralleling the increase in calcium score. Also, the technique has been demonstrated to be an independent predictor of cardiovascular events, thereby potentially refining Framingham risk stratification.[34]

Examination of coronary atherosclerosis: plaque imaging

It has been shown, that the risk of acute coronary syndromes caused by plaque disruption and thrombosis depends on plaque composition rather than stenosis severity.[35,36] In this context, an important advantage of non-invasive coronary angiography with MSCT as compared to conventional coronary angiography is the ability to image the vessel wall. Figure 2 demonstrates evaluation of coronary plaques with 64-slice MSCT. Coronary plaque imaging with MSCT relies on a difference in densities (expressed in Hounsfield Units, HU) in different types of coronary lesions. It has been shown by Schroeder and colleagues that significantly different mean densities of 419±194 HU, 91±21 HU and 14±26 HU can be detected respectively in calcified, intermediate and soft plaques (with intravascular ultrasound serving as standard of reference).[37] Recently Kunimasa et al have demonstrated

that low density coronary plaques detected with 16-slice MSCT were significantly more often observed in patients presenting with acute coronary syndromes as compared to those having stable CAD.[38] Similarly, MSCT allows assessment of coronary artery remodeling. Achenbach et al have demonstrated that the mean remodeling index measured by MSCT was significantly higher in nonstenotic than in stenotic lesions (1.3±0.2 versus 1.0±0.2, $p<0.001$). Moreover, remodeling indices measured by MSCT correlated closely to intravascular ultrasound ($r=0.82$).[39] However, available data on plaque imaging with MSCT are still limited and prospective studies are required whether MSCT can indeed play a role in identification of patients at elevated risk for coronary events based on the plaque distribution and type. Moreover, further distinction of low-density plaques in fibrous and lipid content appears not feasible as their signal intensities on MSCT are highly overlapping.

Additional diagnostic information with MSCT; LV function and perfusion

Image acquisition, reconstruction and post-processing

Assessment of LV function with MSCT is only possible at rest, since repeated scanning during stress and resting conditions is not justifiable due to the high radiation dose. The same set of axial slices acquired during helical scanning of the coronary arteries is used for LV function imaging. For the assessment of LV systolic function, the entire heart is reconstructed in the short-axis plane in 10 or 20 cardiac phases (using a step of 10% and 5% of the R-R interval on the electrocardiogram, respectively) with the various reconstructed slice thickness and reconstruction increment.[40,41] The set of axial images is then transferred to the remote workstation with dedicated software for analysis of global and regional LV systolic function. For LV perfusion analysis, the density of the hypoperfused and normally perfused myocardial areas is assessed and expressed in HU. The hypoperfused areas may be quantitatively assessed with the use of available software. An example of evaluation of global LV systolic function and myocardial perfusion with 64-slice MSCT is provided in Figure 4.

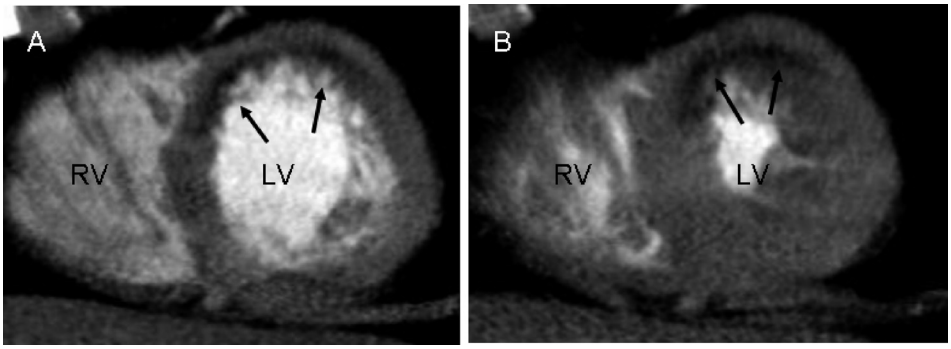

Figure 4. Evaluation of LV function in a patient with a history of anterior myocardial infarction. (A) End-diastolic phase. (B) Myocardial thickening in end-systolic phase. Perfusion defects are seen in anterior segments (arrows), confirming the presence of previous myocardial infarction.
ED, end-diastole; ES, end-systole; LV, left ventricle; RV, right ventricle.

Systolic left ventricular function

In ischemic heart disease cardiac function provides both diagnostic and prognostic information.[42,43] Decreased LV function has been related to worse prognosis after myocardial infarction.

Several studies have shown excellent correlation and agreement between LV volumes and ejection fraction (EF) obtained by MSCT and 2D echocardiography.[41,44-47] Schuijf et al compared global LV systolic function with 4-slice MSCT and 2D echocardiography. Bland-Altman analysis in comparison of LVEF showed a mean difference of -0.48±3.8%, which was not significant from 0.[44] Similarly, another study with 16-slice MSCT showed an excellent correlation (r=0.96) between the two modalities in the evaluation of global LV systolic function.[46] The comparison of global LV systolic function with MRI showed similar results.[41,48] Salm et al demonstrated fair correlation (r=0.86) between 16-slice MSCT and MRI in the assessment of LVEF.[41] Another study by Mahnken and coworkers demonstrated that MSCT multisegmental image reconstruction improved the quantitative assessment of global LV systolic function, as compared to MRI, resulting in better agreement between the two modalities.[48] Besides global LV systolic function, the presence of regional wall motion abnormalities can be assessed from the cine-loop images. In a study with 4-slice MSCT, a good correlation was demonstrated between myocardial wall motion as compared to 2D echocardiography, overall agreement was 88% with a weighted kappa value of 0.84.[45] Sixteen-slice MSCT has shown even better correlation of qualitative assessment of wall motion abnormalities as compared to 2D echocardiography. In a study by Schuijf et al, the

agreement between the two modalities for assessment of regional contractile function was excellent (91%, kappa statistic 0.81).[47] In the comparison of regional systolic LV function detected with MSCT multisegmental reconstruction algorithm and MRI overall agreement was 92.5%.[48] Another study comparing regional wall motion assessed with 16-slice MSCT and MRI showed a good agreement of wall motion scores with kappa value of 0.8.[49]

Although an MSCT scan is not justifiable to solely assess systolic LV function, the functional parameters obtained during the same scan performed for coronary angiography may importantly add to the diagnostic (and potentially prognostic) work-up of patients with suspected or known CAD.

Myocardial perfusion

As described above, only myocardial perfusion at rest may be justifiable, as repeated scanning during stress and resting conditions is associated with a high X-ray dose. Perfusion abnormalities at rest may be observed in the early phase of the contrast bolus. Several reports have evaluated the diagnostic performance of MSCT in the diagnosis of the myocardial infarction. Nikolaou et al observed a sensitivity and specificity of 4-slice MSCT to detect myocardial infarction with invasive ventriculography serving as standard of reference to be 85% and 91%, respectively.[50] Moreover, the authors have demonstrated the ability of MSCT to differentiate old and recent myocardial infarction on the basis of the tissue density expressed in HU, old infarctions having lower CT densities as compared to recently infarcted areas (44±17 HU versus 63±19 HU; p=0.0465).[50] Due to high spatial resolution of MSCT, the differentiation of subendocardial and transmural infarctions is possible, which may have additional prognostic information. Wada et al have demonstrated poor recovery of regional and global systolic left ventricular function in patients having transmural infarction at 6 months after the onset of acute myocardial infarction, whereas the subendocardial infarction group exhibited good recovery of LV function.[51] Sporadic studies have also examined the ability of MSCT to evaluate myocardial viability, based on assessment of myocardial perfusion. Mahnken et al evaluated myocardial perfusion with 16-slice MSCT in the early phase of the contrast bolus and 15 min after contrast injection. An excellent agreement was demonstrated between the infarct size on late enhancement of MRI and late enhancement of MSCT.[52] Theoretically, also evaluation of perfusion during stress may be possible, as was recently explored by Kurata et al in 12 patients, showing an 83% agreement between MSCT and SPECT to detect stress induced (by means of adenosine triphosphate) hypoperfusion areas.[53] However, further evaluation is necessary to define the clinical role of myocardial perfusion assessment with MSCT.

Limitations of MSCT

Despite the enormous development of MSCT technique during the last decade, several important limitations still remain. The newer scanner generations with improving spatial resolution are associated with high radiation. The effective dose of 64-slice MSCT scanner is substantially higher (14 mSv) than that of conventional coronary angiography (6 mSv).[54] MSCT techniques have been developed to reduce radiation exposure, such as the reduction of X-ray tube current at early systolic and diastolic phases of the R-R interval, or the use of prospective triggering for coronary calcium scoring. At present, the technique is therefore not suitable for repeated imaging to monitor disease progression/regression or to allow sequential imaging of LV function during stress and resting conditions. Although the amount of injected iodinated contrast is decreasing with the shorter scan time of the newer scanner generations, the use of contrast limits examination of patients with impaired renal function. A stable and low heart rhythm is an important prerequisite of cardiac MSCT. Although reconstruction algorithms are available to improve image quality in patients with heart rates above 65 beats per minute, artificial lowering of the heart rate is still preferable to obtain best results. Technical advancements, such the introduction of DSCT, may potentially assist in overcoming the need of lowering of heart rate. Also, atrial fibrillation and frequent extrasystoles often require deferring the procedure due to unacceptable motion artefacts. To date, mostly qualitative analysis of coronary stenoses is available and quantitative evaluation needs to be developed and validated. The presence of coronary artery calcifications is another serious limitation for MSCT coronary angiography, hampering precise evaluation of the degree of coronary stenoses. Although the technique allows accurate evaluation of coronary stenoses, its capacity of functional imaging is limited, as compared to radionuclide imaging, MRI and echocardiography which allow evaluation of a wider range of LV functional parameters.

Expert opinion

An alternative, less expensive non-invasive diagnostic test to be used in order to avoid a substantial number of invasive coronary angiographies could have a major impact on clinical practice and cost effectiveness. While diagnostic accuracies and assessability to detect CAD with the first MSCT generations were not sufficient for the application of the technique in clinical practice, the results of the latest 64-slice scanners are excellent. Consistently high negative predictive values have been reported with MSCT, making the technique particularly suitable to exclude CAD in patients with previously unknown CAD at intermediate risk. Nonetheless, most studies have focused on examining patients with high pretest likelihood of CAD thus far and the technique still needs additional validation in patients with lower prevalence of the disease.

Five-year view

Although a possibility to evaluate CAD non-invasively with MSCT is an important development in clinical practice, the evaluation of hemodynamic consequences of CAD (hypoperfusion in ischemic areas and/or induction of systolic LV dysfunction) is essential in the diagnosis of CAD and subsequent choice of therapeutic strategy. Therefore, combined SPECT or PET-CT systems are under development, which will allow fusion of anatomical and functional information on CAD in a given patient. This combination will serve not only for detection of coronary lesions, but also for assessment of hemodynamic consequences of these lesions. Future investigations should be directed to evaluate the integration of these parameters.

Finally, current state-of-the-art MSCT allows non-invasive evaluation of the vessel wall. Evaluation of plaque burden and plaque composition will become increasingly important and will further aid in improved management of patients with CAD.

Key issues

- Multi-slice computed tomography (MSCT), electron beam computed tomography (EBCT) and magnetic resonance imaging (MRI) are the currently available non-invasive imaging modalities to detect coronary artery stenoses.
- The sensitivity and specificity to detect significant stenoses in native coronary arteries with 64-slice MSCT is as high as 93 to 99% and 95 to 97%, respectively, making MSCT the most promising non-invasive imaging modality for anatomical evaluation of coronary artery disease (CAD).
- Evaluation of coronary artery bypass graft occlusion with MSCT is highly accurate; however, the assessment of native coronary arteries of patients after coronary artery bypass graft surgery is problematic due to advanced and diffuse calcifying CAD.
- Precise evaluation of neo-intima hyperplasia in stents remains unlikely with MSCT in the near future due to insufficient spatial resolution of the current scanner generations.
- Evaluation of coronary plaque burden and constitution with MSCT is possible and appears promising.
- MSCT allows evaluation of left ventricular perfusion and systolic function at rest, however, due to high radiation dose associated with repeated scanning, it does not allow detection of CAD by demonstrating myocardial ischemia during stress conditions.
- The major limitations of MSCT are high radiation dose and insufficient temporal resolution, requiring at present a low and stable heart rate during MSCT examination.

Outline of the thesis

The aim of this thesis was to evaluate the role of MSCT in non-invasive imaging of coronary atherosclerosis in patients with suspected CAD. In **Part I**, the ability of MSCT to demonstrate obstructive atherosclerotic lesions in the coronary arteries was explored. The diagnostic accuracy of 64-slice MSCT in detecting obstructive coronary stenoses as compared with conventional coronary angiography was evaluated in **Chapter 2**. In **Chapter 3**, the diagnostic accuracy of 64-slice MSCT coronary angiography in detecting obstructive lesions in male and female patients was investigated. The impact of calcium accumulation in the coronary arteries on the diagnostic accuracy of the previous 16-slice MSCT and the more recent 64-slice MSCT in detecting obstructive lesions was explored in **Chapter 4**. The accuracy of 64-slice MSCT to detect in-stent restenosis was described in **Chapter 5**. In **Chapter 6**, direct comparison between findings on bicycle exercise testing and MSCT coronary angiography is provided.

Part II focuses on characterization of coronary atherosclerotic plaque extent and composition on MSCT. The prognostic value of coronary plaque characteristics on MSCT was explored in **Chapter 7**. Head-to-head comparison of coronary plaque composition between non-invasive MSCT and invasive virtual histology intravascular ultrasound was performed in **Chapter 8**. Coronary plaque characteristics were investigated both on non-invasive MSCT and on invasive virtual histology intravascular ultrasound in patients presenting with acute coronary syndromes and stable CAD in **Chapter 9**. The patterns of coronary atherosclerosis on MSCT in patients with type 2 diabetes were investigated in **Chapters 10** and **11**. Finally, coronary atherosclerosis was explored in men and women with suspected CAD both on MSCT and on gray-scale and virtual histology intravascular ultrasound (**Chapter 12**).

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Part I

Diagnosis of Coronary Artery Disease

Chapter 2

Diagnostic Accuracy of 64-Slice Multislice Computed Tomography in the Noninvasive Evaluation of Significant Coronary Artery Disease

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Abstract

Aims: The purpose of the present study was to determine the diagnostic accuracy of current 64-slice multi-slice computed tomography (MSCT) in the detection of significant coronary artery disease, using conventional coronary angiography as the gold standard.

Methods: In 61 patients scheduled for conventional coronary angiography, 64-slice MSCT was performed and evaluated for the presence of significant (>50% luminal narrowing) stenoses.

Results: One patient had to be excluded because of a heart rate >90 beats/min during data acquisition. In the remaining 60 patients (46 men, 14 women; average age 60±11 years), 854 segments were available for evaluation. Of these segments 842 (99%) were of sufficient image quality. Conventional coronary angiography identified 73 lesions, of which 62 were detected by MSCT. The corresponding sensitivity and specificity were 85% and 97%, respectively. On a patient-per-patient analysis, sensitivity, specificity, and positive and negative predictive values were 94%, 97%, 97%, and 93%, respectively.

Conclusions: The present study confirms that 64-slice MSCT enables the accurate and noninvasive evaluation of significant coronary artery stenoses.

Introduction

In a short period of time, spiral multi-slice computed tomography (MSCT) has rapidly matured into a technique that is on the verge of being used as an alternative modality in the clinical evaluation of patients suspected of having coronary artery stenoses. Although thorough assessment of the entire coronary tree was still problematic with the original 4-slice systems, substantial improvement was obtained with the introduction of 16-slice scanners.[1] In addition, the results of numerous studies comparing MSCT with conventional coronary angiography suggested enhanced sensitivity of the technique as well, with no loss in specificity.[2] Currently, 64-slice MSCT systems are rapidly installed, offering further improved image quality while acquiring data in even shorter periods of time.[3,4] Accordingly, the purpose of the present study was to determine the diagnostic accuracy of current 64-slice MSCT in the detection of significant coronary artery disease (CAD), using conventional coronary angiography as the gold standard.

Methods

Patients and study protocol

The study group consisted of 61 patients who were scheduled for conventional coronary angiography. In addition, MSCT coronary angiography was performed. Patients with contraindications to MSCT were excluded.[5] Conventional catheter-based coronary angiography was performed before or after MSCT and served as the reference standard. All patients gave written informed consent to the study protocol, which was approved by the local ethics committee.

Data acquisition

MSCT was performed using a Toshiba Multi-Slice Aquilion 64 system (Toshiba Medical Systems, Tokyo, Japan), with a collimation of 64x0.5 mm and a rotation time of 0.4 seconds. The tube current was 300 mA, at 120 kV. In obese patients (body mass index ≥30 kg/m^2), parameters were adjusted to 350 mA at 135 kV to improve image quality. Nonionic contrast material was administered in the antecubital vein, with an amount of 80 to 110 ml, depending on the total scan time, and a flow rate of 5.0 ml/s (Iomeron 400, Bracco, Altana, Pharma, Konstanz, Germany). Automated peak enhancement detection in the descending aorta was used for timing of the bolus using a threshold of +100 Hounsfield units. Data acquisition was performed during an inspiratory breath hold of approximately 8 to 10 seconds.

During the MSCT examination, electrocardiography was performed simultaneously for retrospective gating of the data. An initial data set was reconstructed at 75% of the RR interval, with a slice thickness of 0.5 mm and a reconstruction interval of 0.3 mm. In 17 patients, additional reconstructions were explored to obtain more optimal reconstruction phases. Similarly, in case of high-density artifacts, sharper reconstruction kernels were explored to improve image quality. Finally, images were transferred to a remote workstation (Vitrea2, Vital Images, Plymouth, Minnesota) for postprocessing and evaluation. Conventional diagnostic coronary angiography was performed according to standard techniques.

Data analysis

MSCT angiograms were evaluated by an invasive cardiologist with several years of experience in scoring MSCT coronary angiograms. Image analysis was performed blinded to the results of coronary angiography. Three-dimensional volume-rendered reconstructions were used to obtain general information on the status and courses of the coronary arteries. Then the original transaxial slices were inspected for the presence of significant (≥50% reduction of luminal diameter) narrowing, assisted by curved multiplanar reconstructions. Segmentation of the coronary arteries was performed on the basis of the American Heart Association/American College of Cardiology guidelines.[6] Segments containing coronary stents were included in the analysis; the presence of restenosis in a stented segment was identified by reduced or complete absence of contrast within the stent as well as reduced or absent runoff of contrast distally. Conventional angiograms were evaluated by an experienced observer without knowledge of the MSCT data who identified the available coronary segments on the basis of the American Heart Association/American College of Cardiology guidelines.[6] Each segment was then evaluated for the presence of ≥50% diameter stenosis, on the basis of the evaluation of 2 orthogonal views.

Statistical analysis

Obstructive CAD was defined as luminal narrowing of ≥50%. Accordingly, sensitivity, specificity, and positive and negative predictive values (including 95% confidence intervals) for the detection of stenoses ≥50% on conventional angiography were calculated on patient, vessel, and segmental bases. A patient or vessel was classified as correct positive if the presence of any stenosis was identified correctly. In the per vessel analysis, the intermediate branch was considered part of the left circumflex. All statistical analyses were performed using SPSS software version 12.0 (SPSS, Inc., Chicago, Illinois). A value of $p<0.05$ was considered statistically significant.

Results

Patient characteristics

In total, 61 consecutive patients (46 men, 15 women; average age 60±11 years) were included. The average interval between MSCT and conventional angiography was 49±61 days. In 1 patient, the heart rate increased to >90 beats/min during MSCT, rendering the complete data set uninterpretable. The characteristics of the remaining 60 patients are listed in Table 1. In total, CAD was suspected in 25 patients (42%), whereas it was known in 35 patients (58%). A total of 44 stented segments were included in the analysis.

Table 1. Clinical characteristics of the study population (n=60)

Characteristic	Value
Men/women	46/14
Age (yrs) (range)	60±11 (38–80)
Heart rate (beats/min) (range)	60±11 (44–83)
Average calcium score (Agatston) (range)	423±868 (0–6,264)
β-blocking medication	43 (72%)
Diabetes mellitus	6 (10%)
Hypertension*	26 (43%)
Hypercholesterolemia†	27 (45%)
Positive family history	22 (37%)
Current smoking	33 (55%)
Body mass index ≥30 kg/m^2	15 (25%)
No history	25 (42%)
Previous coronary angioplasty	33 (55%)
Previous coronary bypass grafting	0
Previous myocardial infarction	33 (55%)
Anterior wall	26 (79%)
Inferior wall	7 (21%)
No. of coronary arteries narrowed on angiography	
None	14 (23%)
1	26 (43%)
≥1	20 (33%)

* Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.

† Defined as total serum cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or the use of a lipid-lowering agent.

MSCT coronary angiography

In 854 segments evaluated with conventional coronary angiography, a total of 74 significant stenoses was identified. MSCT image quality was insufficient in 12 segments (1.4%) to allow further evaluation. Reasons for uninterpretability were a small contrast-to-noise ratio due to a large body mass index (n=2), extensive calcifications (n=5), and small vessel size (n=5). A total of 6 uninterpretable segments were located in the left circumflex coronary artery (segment 10, n=3; segment 12, n=1; and segment 17, n=2), whereas 4 uninterpretable segments were located in the distal right coronary artery (segment 4, n=2, and segment 16, n=2) and 1 in the first diagonal branch. In the remaining 842 segments, the presence of stenosis was correctly ruled out by MSCT in 755 of 769 segments, while 62 of 73 segments were correctly identified as having significant lesions on MSCT. A total of 14 lesions that were nonsignificant on conventional coronary angiography were overestimated on MSCT, while 11 lesions were falsely deemed to be insignificant. Accordingly, the resulting sensitivity and specificity for the detection of significant lesions were 85% and 98%, respectively, on a segmental level. In the 44 stented segments, 3 of 3 segments with significant in-stent restenosis were correctly detected, whereas the absence of significant lesions was correctly identified in 41 stented segments.

Vessel analysis

Because of extensive calcifications, 1 left circumflex artery was deemed uninterpretable. In the remaining 239 coronary arteries, 46 of 53 coronary arteries were correctly identified as having ≥1 significant lesions, whereas the absence of any stenosis was correctly identified in 179 of 186 vessels, resulting in sensitivity and specificity of 87% and 96%, respectively.

Patient analysis

Conventional coronary angiography identified 31 patients with ≥1 significant lesions. On MSCT, 29 of these patients (94%) were correctly identified. In 1 of these patients, however, a lesion in the left anterior descending coronary artery was misjudged to be significant on MSCT, whereas in fact a lesion in the right coronary artery proved to be significant during conventional coronary angiography. In the remaining patients, the correct lesion was identified on MSCT. An example of a patient with a significant stenosis is provided in Figure 1.

Figure 1. Example of a patient with significant coronary artery disease. (A) Three-dimensional volume-rendered reconstruction providing an overview of the left anterior descending (LAD) and left circumflex (LCx) coronary arteries. An enlargement of the section indicated by the *black arrowhead* (B) demonstrates a significant narrowing in the LAD coronary artery *(black arrowhead)* and, more distally, a small coronary calcification *(white arrowhead)* that can also be observed on the curved multiplanar reconstruction (D). Cross-sectional images (E) confirm the presence of a significant noncalcified lesion. (F) Curved multiplanar reconstruction of the LCx coronary artery without significant lesions. In the right coronary artery (G, 3-dimensional volume-rendered reconstruction; H, curved multiplanar reconstruction), no significant narrowing was observed as well. The findings were confirmed by conventional coronary angiography (C, I).

MSCT correctly ruled out the presence of any significant lesion in 28 of 29 patients (97%). Only 3 patients were incorrectly diagnosed by MSCT. In 1 patient, a significant lesion in the origin of the second diagonal was missed because of the small size of the coronary side branch. In the other patient with false negative MSCT results, significantly diseased left anterior descending and left circumflex arteries were incorrectly classified as having nonobstructive disease.

Finally, in 1 patient who was incorrectly classified as positive, a lesion of approximately 40% located in the left anterior descending artery was overestimated by MSCT. The results of all analyses, including positive and negative predictive values with 95% confidence intervals, are listed in Table 2.

Table 2. Diagnostic accuracy of multi-slice computed tomography (n=60)

Variable	Segmental Analysis	Vessel Analysis	Patient Analysis
Excluded	12/854, 1.4%	1/240, 0.4%	0%
Sensitivity	62/73 (85%, 77–93%)	46/53 (87%, 78–96%)	29/31 (94%, 86–100%)
Specificity	755/769 (98%, 97–99%)	179/186 (96%, 93–99%)	28/29 (97%, 91–100%)
Positive predictive value	62/76 (82%, 73–91%)	46/53 (87%, 78–96%)	29/30 (97%, 91–100%)
Negative predictive value	755/766 (99%, 98–100%)	179/186 (96%, 93–99%)	28/30 (93%, 84–100%)
Diagnostic accuracy	817/842 (97%, 96–98%)	225/239 (94%, 91–97%)	57/60 (95%, 89–100%)

Discussion

On a segmental level, a diagnostic accuracy of 97% was observed. It is important that only 12 segments (1%) could not be evaluated for the presence or absence of significant lesions because of insufficient image quality. In addition, an excellent specificity of 98% was observed, with a somewhat lower sensitivity of 85%, on a segmental basis. Nonetheless, from a clinical point of view, data regarding the performance on a patient rather than a segmental basis are preferred, because the selection of patients needing further invasive evaluation or intervention will be based on these findings. In the present study, a sensitivity of 94% was noted, with a corresponding specificity of 97%, in the detection of patients with obstructive CAD. Thus, in contrast to several previous studies,[4,7] no loss in specificity was observed when shifting from a segmental to a patient analysis. The current observations are in line with the few initial investigations with 64-slice MSCT that have been published thus far.[3,4,8] Similar sensitivity and specificity of 86% and 95%, respectively, on a segmental basis were reported by Raff et al,[7] who performed 64-slice MSCT in 70 patients. More recently, results in 52 patients presenting with a wide range of clinical conditions were

reported by Mollet et al.[4] As a result of the highly symptomatic population included, a greater sensitivity (100%) with somewhat lower specificity(92%) was obtained.

Because the purpose of the present study was to compare the diagnostic accuracy of MSCT with that of invasive coronary angiography, only patients with a relatively high likelihood of having significant stenoses were included. As a result, only 42% of included patients presented without known CAD. Although this percentage still compares favorably with most of the other available data on MSCT coronary angiography, it stipulates the current lack of data in populations with lower CAD prevalence. Considering that noninvasive coronary angiography is most likely to be used in these particular populations to allow the definite exclusion of significant CAD, data on the performance of MSCT in these populations are needed.

Despite rapid technologic advancements, several limitations inherent to MSCT remain. First, a stable and preferably low heart rate remains essential for high-quality MSCT images, and the administration of β blockers before the examination is often needed. Second, the current lack of validated quantification algorithms for MSCT represents another important issue. Although visual evaluation will be sufficient in most segments, more precise assessment of the degree of luminal narrowing will be needed in a considerable number of examinations. However, as shown by Leber et al,[3] the ability to visually quantify the grade of luminal obstruction on MSCT remains limited, even with 64-slice technology. Indeed, also in the present study, the degree of stenosis was incorrectly estimated as either more or <50% diameter narrowing in 2 patients, resulting in false diagnoses, although in fact the presence of lesions was correctly identified. Accordingly, the quantification of MSCT coronary angiography is likely to provide enhanced diagnostic accuracy while improving the reproducibility of the technique, and further investments in the development of such algorithms are needed. Finally, the radiation burden of MSCT remains of concern.

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Chapter 3

Gender Influence on the Diagnostic Accuracy of 64-Slice Multislice Computed Tomography Coronary Angiography for Detection of Obstructive Coronary Artery Disease

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Abstract

Aims: To compare the diagnostic accuracy of 64-slice multi-slice computed tomography (MSCT) coronary angiography between female and male patients using conventional coronary angiography as the reference standard.

Methods: 103 consecutive patients (51 men, 52 women, mean age 60±10 years) with known and suspected coronary artery disease underwent 64-slice MSCT. Main outcome measure was diagnostic accuracy of 64-slice MSCT to detect obstructive (≥50% luminal narrowing) stenoses in men and women.

Results: One male and two female patients were excluded from the analysis due to non-diagnostic MSCT scans as a result of elevated heart rate and breathing during the scan. Accordingly, on segmental level, 728 of 762 coronary segments were of sufficient quality in women (96% (95% CI 95%-97%)) and 704 of 723 segments were interpretable in men (97% (95% CI 96%-98%)). In the remaining 100 patients included in the further analyses, the sensitivity and specificity on a segmental level in women and men was 85% (95% CI 75%-95%) versus 85% (95% CI 78%-92%) and 99% (95% CI 98%-100%) versus 99% (95% CI 98%-100%), respectively. On a patient level, the sensitivity in women and men was 95% (95% CI 87%-100%) versus 100%, specificity 93% (95% CI 83%-100%) versus 89% (95% CI 74%-100%), positive predictive value 91% (95% CI 79%-100%) versus 94% (95% CI 86%-100%), and negative predictive value 96% (95% CI 89%-100%) versus 100%, respectively.

Conclusions: The findings of the study confirm the high diagnostic accuracy of 64-slice MSCT coronary angiography in both male and female patients.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality in the western world. Although in men mortality due to CAD appears to be declining, an increase has recently been observed in women.[1-3] Unfortunately, accurate diagnosis of CAD may be more challenging in women as compared to men. Limited exercise capacity is frequently encountered in women, resulting in inconclusive exercise electrocardiography results. In addition higher false positive rates may be observed.[2] As a result, a considerable proportion of women are unnecessarily referred for conventional invasive coronary angiography, and obstructive CAD is absent in nearly half of women undergoing invasive coronary angiography.[2]

Multi-slice computed tomography (MSCT) coronary angiography allows direct non-invasive visualization of coronary arteries and accurate detection of obstructive lesions as compared to invasive coronary angiography. Indeed, the reported mean sensitivity and specificity of 64-slice MSCT is 87% and 96%, respectively.[4] In particular, the negative predictive value was extremely high (approaching 100%) allowing reliable exclusion of CAD. Nevertheless, to date substantial under-representation of women has been observed in MSCT diagnostic accuracy studies, with approximately only 20% of included patients being female.[4,5]

Accordingly, the purpose of the study was to compare the diagnostic accuracy of current 64-slice MSCT coronary angiography between males and females using conventional coronary angiography as the reference standard.

Methods

Study population

A total of respectively 51 and 52 consecutive male and female patients presenting with known and suspected CAD (based on chest pain complaints and presence of risk factors of CAD) and scheduled for conventional invasive coronary angiography were included in the study. The aim of the study inclusion was to reach a 50% distribution of both genders in the total patient population. The median interval between conventional and MSCT coronary angiography was 4 (0-8) weeks. No intervening changes in the clinical condition of the patients occurred between the two examinations. Only patients with sinus rhythm and without contraindications to iodinated contrast medium were included in the study. All patients gave informed consent, which was approved by local ethics committee.

MSCT data acquisition

All MSCT coronary angiography examinations were performed with an Aquilion 64 system (Toshiba, Tokyo, Japan). If the heart rate was ≥65 beats/min oral beta-blockers (metoprolol, 50 or 100 mg, single dose, one hour prior to the examination) were provided if tolerated. The following parameters were used for 64-slice MSCT coronary angiography: collimation 64x0.5 mm, tube rotation time 400, 450 or 500 ms depending on the heart rate, tube current 300 or 350 mA, tube voltage 120 kV. Non-ionic contrast material was administered in the antecubital vein with an amount of 90 to 100 ml, depending on the total scan time, and a flow rate of 5 ml/sec (Iomeron 400, Bracco Altana Pharma, Konstanz, Germany), followed by a saline solution flush of 50 ml. Automated bolus-tracking in the aortic root was used for timing of the scan. All images were acquired during a single inspiratory breath hold of approximately 10 s, with simultaneous registration of the patient's electrocardiogram. With the aid of a segmental reconstruction algorithm, data of one, two or three consecutive heartbeats were used to generate a single image.

Images were reconstructed in the cardiac phase showing least motion artefacts. Typically this was an end-diastolic phase, however additional reconstructions were made throughout the entire cardiac cycle, if needed. Reconstructed images were transferred to a remote workstation for post-processing.

MSCT data analysis

MSCT angiograms were evaluated in consensus by two experienced observers, who were unaware of the results of conventional coronary angiography. The presence of obstructive lesions (≥50% luminal narrowing) was evaluated by scrolling through axial images, followed by visual assessment of curved multiplanar reconstructions in at least two orthogonal planes. Patients were excluded from the analysis of diagnostic accuracy of MSCT coronary angiography in case of 1. an uninterpretable proximal or mid segment or 2. more than two uninterpretable segments in the vessel. However, these patients were included in the analysis of interpretability. Coronary stents were included in the analysis and restenosis was defined as reduced or complete absence of contrast within the stent as well as reduced or absent contrast runoff distally.

Conventional invasive coronary angiography

Conventional invasive coronary angiography was performed according to the standard protocols. Coronary angiograms were visually assessed by one experienced observer who was unaware of the results of MSCT coronary angiography. Each coronary segment

as defined by the American Heart Association/American College of Cardiology modified 17 segment model was evaluated in two orthogonal views for the presence of ≥50% diameter stenosis.

Statistical analysis

Continuous variables are expressed as mean (standard deviation) and compared between the two groups by t-test for independent samples. When not normally distributed, continuous data are expressed as median (interquartile range) and compared between the two groups by non-parametric Mann-Whitney test. Categorical variables are expressed as absolute numbers (percentages) and compared between the two groups by Chi-square test or Fisher's exact test for sparse data. The sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and diagnostic odds ratio were calculated based on the rates of true positive, true negative, false positive and false negative test results.[6] The interpretability and diagnostic accuracy to detect stenoses of ≥50% were compared between the two groups using the 95% confidence intervals (95% CI). Conventional coronary angiography served as the reference standard. Diagnostic accuracy was evaluated on segmental, vessel and patient basis. A vessel or patient was assigned as correct positive if at least one obstructive lesion in the vessel or patient were detected correctly. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA). P-values <0.05 were considered as statistically significant. The study conforms to the criteria as set in the STARD initiative.[7]

Results

Patient characteristics

An elevated heart rate and breathing during the scan rendered examinations of one male and two female patients non-diagnostic and as a consequence these patients were excluded from the MSCT diagnostic accuracy analysis. However, these patients were included in the evaluation of interpretability of the study results. The clinical characteristics of the remaining 100 patients included in the study of diagnostic accuracy (50 men and 50 women, mean age 60±10 years) are presented in Table 1. In total, 36 (36%) patients presented with a previous history of CAD (myocardial infarction and/or percutaneous coronary intervention), the remaining 64 (64%) patients presented with suspected CAD. Women showed a higher prevalence of family history of CAD and lower overall Agatston calcium score than men.

Table 1. Characteristics of the study population

	Total population (n=100)	Women (n=50)	Men (n=50)
Age (mean±SD)	60±10	60±10	60±11
History of CAD:			
Previous PCI	34 (34%)	17 (34%)	17 (34%)
Previous MI	31 (31%)	16 (32%)	15 (30%)
Risk factors for CAD:			
Type 2 diabetes mellitus	21 (21%)	9 (18%)	12 (24%)
Hypercholesterolemia	62 (62%)	28 (56%)	34 (68%)
Arterial hypertension	58 (58%)	31 (62%)	27 (54%)
Family history of CAD*	46 (46%)	29 (58%)	17 (34%)
Smoking	46 (46%)	25 (50%)	21 (42%)
Obesity	21 (21%)	8 (16%)	13 (26%)
Medications:			
ACEI	44 (44%)	21 (42%)	23 (46%)
Beta-blockers	61 (61%)	31 (62%)	30 (60%)
Aspirin	64 (64%)	32 (64%)	32 (64%)
Statins	55 (55%)	23 (46%)	32 (64%)
No. of diseased vessels:			
0	46 (46%)	28 (56%)	18 (36%)
1	20 (20%)	9 (18%)	11 (22%)
2	24 (24%)	11 (22%)	13 (26%)
3	10 (10%)	2 (4%)	8 (16%)
MSCT:			
Total Agatston calcium score (median, 25^{th}-75^{th} percentile)†	216 (7-530)	78 (0-321)	387 (155-715)

* p=0.016 between women and men.

† p<0.0001 between women and men.

Data are absolute numbers (%), unless otherwise indicated.

ACEI, angiotensin converting enzyme inhibitors; CAD, coronary artery disease; MI, myocardial infarction; MSCT, multi-slice computed tomography; PCI, percutaneous coronary intervention.

MSCT coronary angiography

All patients

On the basis of conventional invasive coronary angiography, obstructive lesions were present in 54 (54%) patients (one vessel disease was observed in 20 patients, two vessel disease – in 24 patients, three vessel disease – in ten patients) (Table 1).

Table 2. Diagnostic accuracy of 64-slice MSCT in the entire study population

	Segmental basis	Vessel basis	Patient basis
Interpretable	1432/1485 (96, 95-97)	400/412 (97, 95-99)	100/103 (97, 94-100)
Sensitivity	122/143 (85, 80-91)	90/100 (90, 84-96)	53/54 (98, 95-100)
Specificity	1276/1289 (99, 98-100)	290/300 (97, 95-99)	42/46 (91, 83-99)
PPV	122/135 (90, 85-95)	90/100 (90, 84-96)	53/57 (93, 86-100)
NPV	1276/1297 (98, 97-99)	290/300 (97, 95-99)	42/43 (98, 94-100)
Positive LR (LR, 95% CI)	84.59 (49.04-145.91)	27 (14.63-49.84)	11.29 (4.42-28.81)
Negative LR (LR, 95% CI)	0.15 (0.10-0.22)	0.1 (0.06-0.19)	0.02 (0.00-0.14)
Diagnostic OR (OR, 95% CI)	570.23 (279.91-1160.87)	261 (106.1-642.09)	556.5 (71.37-3921.83)

Data are absolute values used to calculate percentages unless otherwise indicated. Data in parentheses are the percentages with 95% confidence intervals unless otherwise indicated.
CI, confidence intervals; LR, likelihood ratio; MSCT, multi-slice computed tomography; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

The results of diagnostic accuracy to detect obstructive lesions with 64-slice MSCT are depicted in Table 2. After exclusion of 13 segments due to small vessel size and 40 segments due to motion artefacts, 1432 coronary segments (38 segments with stents) were included in the analysis. Of 143 obstructive lesions detected on conventional invasive coronary angiography, 122 were correctly identified on MSCT, and disease was correctly ruled-out in 1276 segments out of 1289, resulting in sensitivity of 85% (95% CI 80%-91%), specificity of 99% (95% CI 98%-100%), positive likelihood ratio of 84.59 (95% CI 49.04-145.91), negative likelihood ratio of 0.15 (95% CI 0.10-0.22), and diagnostic odds ratio of 570.23 (95% CI 279.91-1160.87). In total, 12 coronary vessels were excluded from the analysis. In the included vessels, the overall sensitivity was 90% (95% CI 84%-96%) and the specificity was 97% (95% CI 95%-99%). All but one patients with obstructive CAD on conventional invasive coronary angiography and included in the analysis were correctly identified by MSCT to have at least one obstructive lesion, resulting in sensitivity of 98% (95% CI 95%-100%). Four patients were identified as false positive, resulting in specificity of 91% (95% CI 83%-99%).

Women versus men

An example of obstructive CAD on 64-slice MSCT in a female patient is provided in Figure 1. After exclusion of 6 segments due to small vessel size and 28 segments due to motion artefacts, 728 (96%) coronary segments (18 segments with stents) were included in the female population. In the male population, 7 segments were excluded due to small vessel size and 12

segments due to motion artefacts, resulting in 704 (97%) segments included in the study (20 segments containing stents). As can be derived from Table 3, no significant differences were observed between the number of interpretable segments in men and women. Moreover, similar diagnostic accuracy was found on a segmental, vessel and patient basis. On a segmental basis, the sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio to detect obstructive stenoses in women were 85% (95% CI 75%-95%), 99% (95% CI 98%-100%), 82.98 (95% CI 39.34-174.99), 0.15 (95% CI 0.07-0.29), and 563.12 (95% CI 191.21-1659.22), respectively, and 85% (95% CI 78%-92%), 99% (95% CI 98%-100%), 86.54 (95% CI 38.86-192.72), 0.15 (95% CI 0.09-0.24), and 581.46 (95% CI 220.59-1524.5), respectively, in men, not significantly different between the two patient populations. No significant differences were observed between the number of interpretable vessels and patients in women and men. When shifting to vessel and patient level, both in men and women the sensitivity increased, while specificity decreased slightly. No significant influence of gender was observed (sensitivity, specificity, positive and negative likelihood ratios in women 95% (95% CI 87%-100%), 93% (95% CI 83%-100%), 13.36 (95% CI 3.50-50.97), and 0.05 (95% CI 0.01-0.33)), respectively, and 100%, 89% (95% CI 74%-100%), 9 (95% CI 2.44-33.24), and 0 (95% CI 0-0.09)), respectively, in men).

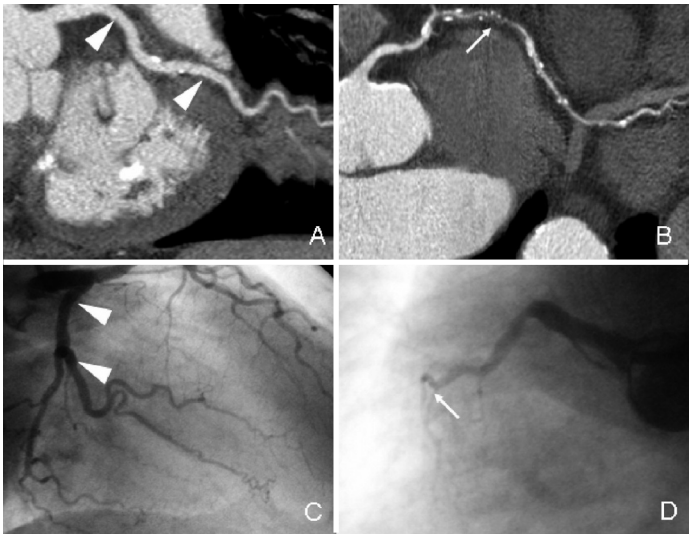

Figure 1. An example of a woman with obstructive coronary artery disease demonstrated with 64-slice multi-slice computed tomography (MSCT) coronary angiography. (A) Multiplanar reconstruction (MPR) of the left circumflex coronary artery (arrowheads) with minimal irregularities of the artery wall. (B) MPR of the right coronary artery showing occlusion in the middle part of the vessel (arrow). The distal part of the artery is filled through collaterals. (C, D) The findings were confirmed by conventional coronary angiography (arrowheads and arrow).

Table 3. Diagnostic accuracy of 64-slice MSCT in women versus men

	Women	Men
Segmental basis:		
Interpretable	728/762 (96, 95-97)	704/723 (97, 96-98)
Sensitivity	41/48 (85, 75-95)	81/95 (85, 78-92)
Specificity	673/680 (99, 98-100)	603/609 (99, 98-100)
PPV	41/48 (85, 75-95)	81/87 (93, 88-98)
NPV	673/680 (99, 98-100)	603/617 (98, 97-99)
Positive LR (LR, 95% CI)	82.98 (39.34-174.99)	86.54 (38.86-192.72)
Negative LR (LR, 95% CI)	0.15 (0.07-0.29)	0.15 (0.09-0.24)
Diagnostic OR (OR, 95% CI)	563.12 (191.21-1659.22)	581.46 (220.59-1524.5)
Vessel basis:		
Interpretable	200/208 (96, 93-99)	200/204 (98, 96-100)
Sensitivity	34/37 (92, 83-100)	56/63 (89, 81-97)
Specificity	158/163 (97, 94-100)	132/137 (96, 93-99)
PPV	34/39 (87, 76-98)	56/61 (92, 85-99)
NPV	158/161 (98, 96-100)	132/139 (95, 91-99)
Positive LR (LR, 95% CI)	29.96 (12.57-71.38)	24.36 (10.26-57.83)
Negative LR (LR, 95% CI)	0.08 (0.03-0.25)	0.12 (0.06-0.23)
Diagnostic OR (OR, 95% CI)	358.13 (84.76-1494.5)	211.2 (65.48-679.41)
Patient basis:		
Interpretable	50/52 (96, 91-100)	50/51 (98, 94-100)
Sensitivity	21/22 (95, 87-100)	32/32 (100, NA)
Specificity	26/28 (93, 83-100)	16/18 (89, 74-100)
PPV	21/23 (91, 79-100)	32/34 (94, 86-100)
NPV	26/27 (96, 89-100)	16/16 (100, NA)
Positive LR (LR, 95% CI)	13.36 (3.50-50.97)	9 (2.44-33.24)
Negative LR (LR, 95% CI)	0.05 (0.01-0.33)	0 (0-0.09)
Diagnostic OR (OR, 95% CI)	273 (27.14-2464.86)	NA

Data are absolute values used to calculate percentages unless otherwise indicated. Data in parentheses are the percentages with 95% confidence intervals unless otherwise indicated.

CI, confidence intervals; LR, likelihood ratio; MSCT, multi-slice computed tomography; NA, not applicable; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

Discussion

The present study demonstrated a high diagnostic accuracy of 64-slice MSCT coronary angiography in both men and women with no significant differences in accuracy between women and men on a segmental, vessel and patient basis.

On a segmental level, the sensitivity in the whole study population was 85% with specificity as high as 99%, while only 4% of coronary segments were excluded from the analysis. These findings are in line with the previously published data of the study populations composed of mainly male patients.[4,8-14] Indeed, in previous studies of patients with similar CAD prevalence (>50%) as compared to the present study, the reported sensitivity on a segmental level ranged between 85% to 99% and the specificity varied from 94% to 98%.[8-14] Moreover, in a recently published meta-analysis including 9 studies and 544 patients, the mean sensitivity and specificity of 64-slice MSCT coronary angiography to detect obstructive lesions were 87% and 96%, respectively.[4] When shifting to a patient level however, the sensitivity increased to 98% with a slight decrease in specificity to 91% while importantly the negative predictive value remained high (98%). In clinical practice, a patient based analysis is even more relevant, since selection (or exclusion) of patients for further invasive diagnostic studies followed by therapeutic interventions are based on the latter.

No significant differences in the diagnostic accuracy of MSCT coronary angiography were demonstrated between women and men with similar age and clinical presentation. Importantly, non-invasive angiography by MSCT may be particularly beneficial in women, since previous studies have shown that absence of obstructive CAD on conventional coronary angiography is demonstrated in approximately half of symptomatic women as compared to only 17% in age-matched men.[2,15,16] Similarly, the ability to predict CAD based on clinical symptoms appears to be limited in women of all age groups. Indeed, the observed disease prevalence on conventional coronary angiography in 55-65 year old women has been shown to be half of expected based on the likelihood of CAD determined by the Diamond and Forrester method.[2] Moreover, traditional non-invasive tests may be suboptimal in women in the detection of CAD as compared to men. Indeed, for exercise electrocardiography a lower sensitivity and specificity of 60% and 70% has been shown in women as compared to men, in whom sensitivity and specificity are approximately 80%.[2] Similarly, the sensitivity and specificity of stress myocardial perfusion imaging in women are 81% and 66%, respectively.[2,17] Accordingly, non-invasive coronary angiography with MSCT, which allows direct visualization and exclusion of coronary artery stenoses with high

accuracy, may be a useful tool in the clinical work-up of women with suspected CAD. Importantly, in case of a normal MSCT scan, the likelihood of obstructive stenoses in the epicardial coronary arteries is extremely low, since the negative predictive value of the technique exceeds 95%. Accordingly, the technique allows accurate rule-out of obstructive CAD in women.

Study limitations

Several limitations of the study should be acknowledged. Only patients scheduled for conventional coronary angiography were included in the study, resulting in high disease prevalence (44% in women and 64% in men). Therefore, the findings of the study need to be validated in population with lower disease prevalence.

In addition, MSCT has several important limitations in general. First, the radiation dose of 64-slice MSCT is 12 to 15 mSv with an estimated radiation dose even higher in women.[18] Another important limitation of MSCT coronary angiography is that it does not provide information on functional significance of the detected stenoses and functional testing remains necessary in case of observed stenoses.

Conclusion

The findings of the present study confirm the high diagnostic accuracy of current non-invasive 64-slice MSCT coronary angiography in male as well as in female patients.

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Chapter 4

Impact of Coronary Calcium Score on Diagnostic Accuracy of Multislice Computed Tomography Coronary Angiography for Detection of Coronary Artery Disease

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Abstract

Background: The impact of coronary calcium score on diagnostic accuracy of multi-slice computed tomography (MSCT) to detect obstructive coronary stenoses remains controversial.

Methods: Forty-one patients (Agatston score 340±530 (range 0–2546)) with coronary artery disease were examined with 16-slice MSCT and 60 patients (Agatston score 446±877 (range 0–6264)) with 64-slice MSCT. CT scans were analyzed with invasive coronary angiography (CA) as standard of reference. Lesions with ≥50% luminal narrowing were considered obstructive.

Results: In total, 9% and 2% of uninterpretable segments were excluded from analysis in patients examined with 16- and 64-slice MSCT, respectively. On segment-basis, the percentage of false negative segments in the groups with Agatston scores 0-100, 101-400 and >400 with 16-slice MSCT were 0%, 5.3%, 2.9% (p=0.0005), other comparisons of false positive and negative segments were not significant. The sensitivity and specificity on vessel- and patient-basis with 16- and 64-slice MSCT were not significantly different in different calcium score groups.

Conclusions: A slight impact of coronary calcium was observed on the diagnostic accuracy of 16-slice MSCT CA on a segment-basis with no significant impact on a vessel- and patient-basis. No significant impact of coronary calcium was observed on the diagnostic accuracy of 64-slice MSCT CA on a segment-, vessel- and patient-basis.

Introduction

Over the past years, multi-slice computed tomography (MSCT) has been demonstrated as a feasible alternative to invasive coronary angiography, allowing noninvasive evaluation of the coronary arteries.[1-4] Rapid development of the technique resulted in superior visualization of the coronary arteries and the initial reports published with 64-slice MSCT show extremely promising results, with sensitivities and specificities ranging from 94% to 99% and 95% to 97%, respectively.[3-4] With the first generations of MSCT scanners, severe coronary calcifications have been recognized as an important factor hampering precise evaluation of coronary artery stenoses thereby limiting diagnostic accuracy.[5] Accordingly, coronary calcifications may represent an important limitation of the technique. Nonetheless, accurate assessment in the presence of elevated coronary artery calcium scores is important as increased prevalence and extent of coronary artery calcifications have been observed in certain populations including the elderly and diabetic patients.[6,7] With the introduction of 16-slice MSCT, image quality has improved significantly due to superior spatial and temporal resolution. However, contradictory results of the effect of coronary artery calcium score on diagnostic accuracy of 16-slice MSCT CA have been reported, with some studies showing no influence[8] and others reporting high numbers of uninterpretable or incorrectly diagnosed coronary lesions due to severe coronary calcifications.[9,10] Moreover, data on the influence of coronary calcium score on diagnostic accuracy of 64-slice MSCT are limited. The purpose of the present study was to evaluate the impact of coronary artery calcium score on the diagnostic accuracy of 16- and 64-slice MSCT.

Methods

Patients and study protocol

A total of 101 patients who were already scheduled for conventional CA having presented with known or suspected coronary artery disease were included in the study. All patients underwent MSCT followed by conventional CA for the evaluation of the coronary arteries; 41 patients (30 men, mean age 58±13 years) were examined with 16-slice MSCT and 60 consecutive patients (47 men, mean age 60±11 years) have undergone examination with 64-slice MSCT. The median interval between conventional CA and MSCT was 4 weeks (range 0-27 weeks). No intervening changes in clinical conditions in patients have occurred between the 2 examinations. Only patients with regular heart rate in sinus rhythm and without contraindications to iodinated contrast medium have been included. All patients gave written informed consent to the study protocol, which was approved by the local ethics committee.

MSCT data acquisition

The MSCT examinations were performed with a 16- and 64-slice Toshiba Multi-slice Aquilion systems (Toshiba Medical Systems, Tokyo, Japan). No additional beta blockers were administered before the examinations. A prospective coronary calcium scan was performed prior to MSCT angiography with the same parameters for 16- and 64-slice MSCT scanner: collimation 4x3.0 mm, gantry rotation time 500 ms, the tube voltage and tube current 120 kV and 200 mA, respectively. The temporal window was set at 75% after the R-wave for electrocardiographically triggered prospective reconstruction.

The 16-slice MSCT CA scan was performed after the intravenous administration of 120 to 150 ml iodinated contrast medium depending on the total scan time, with an injection rate of 4 ml/s through the antecubital vein (Xenetix 300, Guerbet, Aulnay S. Bois, France). The scan parameters were as follows: collimation 16 x 0.5 mm, tube rotation time 400, 500 or 600 ms, depending on the heart rate, the tube current 250 mA and tube voltage 120 mV. The 64-slice MSCT CA scan was performed with a collimation of 64x0.5 mm and a tube rotation time of 400, 450 or 500 ms, depending on the heart rate. The tube current was 300 mA, at 120 kV. Non-ionic contrast material was administered in the antecubital vein with an amount of 80 to 110 ml, depending on the total scan time, and a flow rate of 5 ml/sec (Iomeron 400, Bracco Altana Pharma, Konstanz, Germany). Automated detection of peak enhancement in the aortic root was used for timing of the scan. All images were acquired during an inspiratory breath hold of approximately 20 s and 10 s with 16- and 64-slice MSCT respectively, with simultaneous registration of the patient's electrocardiogram. With the aid of a segmental reconstruction algorithm, data of one, 2 or three consecutive heartbeats were used to generate a single image.

To evaluate the presence of coronary artery stenoses, separate reconstructions in diastole (typically 75% of the cardiac cycle) were generated with a reconstructed section thickness of either 0.3 mm or 0.4 mm. If motion artefacts were present, additional reconstructions were made in different time points of the R-R interval. Axial data sets were transferred to a remote workstation (Vitrea2, Vital Images, Plymouth, Minn, USA) for post-processing and subsequent evaluation.

MSCT data analysis

Coronary calcium score

Coronary calcium score was assessed with the application of dedicated software (Vitrea2, Vital Images, Plymouth, Minn, USA). Coronary calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU. In addition to per vessel measurements, an overall Agatston score was recorded for each patient. For precise evaluation of calcium score, all coronary segments were visually inspected and care was taken to avoid inclusion of coronary stents.

Coronary angiography

MSCT angiograms performed with 16- and 64-slice scanners were retrospectively evaluated by the same 2 experienced observers (within a limited period of time), who were unaware of the results of the conventional angiogram. The following protocol was applied in the evaluation of the MSCT coronary angiograms: the 3D volume rendered images were evaluated first to get a general impression of the course and status of left and right coronary arteries. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification and regarded as interpretable or not by visual inspection. Subsequently, the interpretable segments were evaluated for the presence of obstructive stenoses (≥50% reduction of lumen diameter) both scrolling through the axial images and inspecting curved multiplanar reconstructions.

Conventional coronary angiography

Conventional coronary angiography was performed according to standard protocols. For vascular access, the femoral approach with the Seldinger technique was applied. Coronary angiograms were visually evaluated by consensus of 2 experienced observers blinded to the MSCT data.

Statistical analysis

Continuous data are expressed as mean±standard deviation. The differences in descriptives between the 2 patient cohorts examined with 16- and 64-slice MSCT were tested with T-test. Coronary segments and patients were divided into 3 groups according to overall Agatston score (0-100, 101-400 and >400). The differences of continuous variables between the 3 groups were tested with one way Anova test. In case of significant differences, the differences were further assessed with Post Hoc (Bonferroni) test. Analysis of impact of calcium score on diagnostic accuracy of MSCT CA was performed on 3 levels: segment by segment, vessel by vessel and patient by patient. The percentages of false positive and false negative segments were compared using Fisher's exact test and the number of interpretable segments was compared with Chi-square test. Sensitivity, specificity, positive and negative predictive values for the detection of ≥50% luminal narrowing in coronary arteries is expressed as percentages with 95% confidence intervals. The p value of 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA).

Results

In total, 102 patients were enrolled in the study. MSCT was successfully performed in 101 patients. One patient has been excluded from the analysis because of insufficient image quality due to elevated heart rate during the scan. Main characteristics of the study population are listed in Table 1.

Table 1. Descriptives of the study population

Variable	Agatston score 0-100	Agatston score 101-400	Agatston score >400
16-slice Multi-slice Computed Tomography Coronary Angiography			
Coronary segments in men/women	125/94	128/41	105/0
Mean age (yrs) *	51±15	62±11	66±7
Mean heart rate (beats/min)	72±13	65±16	70±18
Mean Agatston score	18±21 (0-81)	281±100 (102–397)	1077±731 (428–2546)
Mean BMI (kg/m²)	27±5	26±4	27±5
64-slice Multi-slice Computed Tomography Coronary Angiography			
Coronary segments in men/women	188/65	183/83	239/42
Mean age (yrs) *	57±9	57±10	66±9
Mean heart rate (beats/min)	59±11	57±14	61±11
Mean Agatston score	14±21 (0-70)	213±74 (111–336)	1088±1306 (410–6264)
Mean BMI (kg/m²)	27±3	29±4	27±3

* $p<0.05$

BMI, body mass index; values in parentheses represent range.

Fifty-seven (57%) patients had known CAD: 53 (53%) patients had a history of myocardial infarction and 56 (56%) had previous percutaneous coronary intervention. Known CAD was present in 23 (56%) patients examined with 16-slice MSCT and 34 (57%) who underwent 64-slice MSCT CA. The prevalence of CAD risk factors was as follows: 21 (21%) patients had diabetes mellitus, 57 (57%) hypercholesterolemia, 51 (51%) hypertension, 38 (38%) had a family history of CAD, and 49 (49%) had a history of current or previous smoking. There were no significant differences in the prevalence of risk factors between the two patient populations. Thirty-two (78%) patients examined with 16-slice MSCT and 43 (72%) examined with 64-slice MSCT ($p=0.47$) used beta-blocking agents as part of their baseline treatment. No significant differences were observed between the 2 patient cohorts examined with 16- and 64-slice MSCT in age and body mass index. However, a significant difference in mean heart rate during data acquisition was noted between the 2 groups of patients with low overall Agatston scores examined with different MSCT scanners. The mean Agatston score in the overall population was 340±530 (range 0–2546) and 446±877 (range 0–6264) for the patients examined with 16- and 64-slice MSCT, respectively. Examples of heavily calcified and noncalcified coronary lesions are provided in Figure 1 and Figure 2.

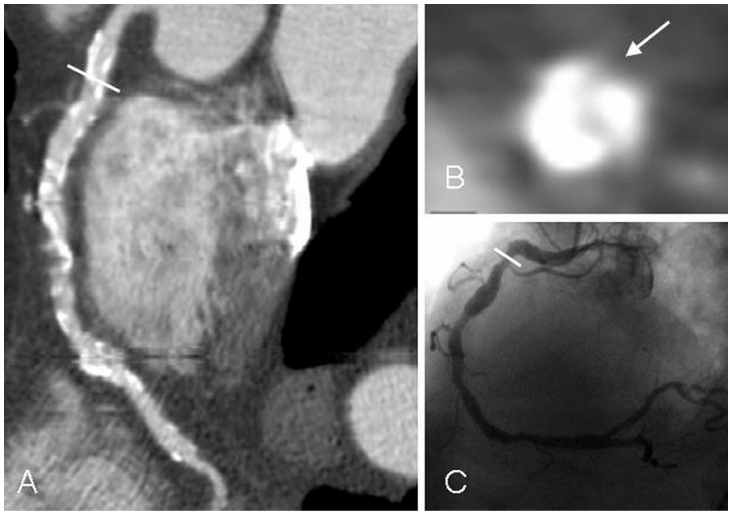

Figure 1. Example of evaluation of stenoses in highly calcified right coronary artery (RCA). (A) Curved multiplanar reconstruction of the RCA is shown, demonstrating multiple obstructive stenoses. Cross sectional reconstruction perpendicular to centerline of the RCA (B) demonstrates highly calcified coronary plaque in the proximal segment of the RCA (corresponding sites in the longitudinal view of the RCA are depicted in (A) and (C)). Invasive coronary angiography confirmed multiple obstructive stenoses in the RCA (C).

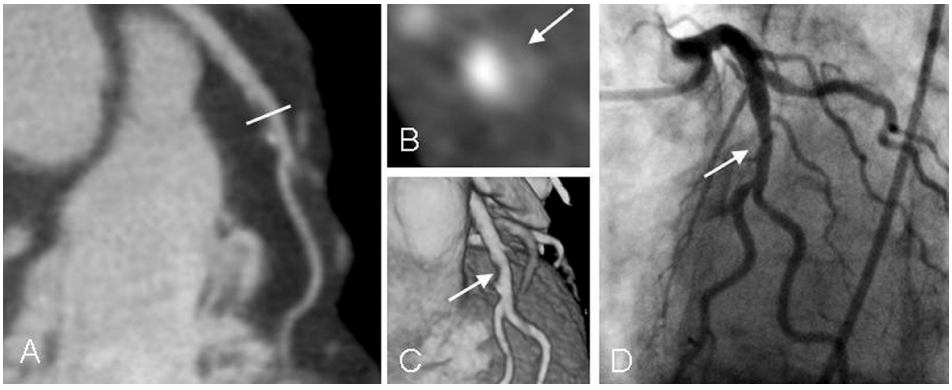

Figure 2. Example of evaluation of stenosis due to a coronary plaque with minimal calcification in the left anterior descending (LAD) coronary artery. (A) Curved multiplanar reconstruction demonstrates a non-obstructive stenosis in the middle part of the vessel. (B) The corresponding cross sectional reconstruction. The same lesion was observed on the three dimensional volume rendered reconstruction (C). Findings were confirmed by conventional coronary angiography (D).

Evaluation of impact of calcium on diagnostic accuracy of MSCT CA: segment by segment analysis

Out of 570 coronary segments of 41 patients examined with 16-slice MSCT, 30 stented segments and 47 uninterpretable coronary segments due to calcium unrelated reasons were excluded, resulting in 493 segments included in the analysis. Reasons for uninterpretability were small vessel size (n=16), motion artefacts (n=13), insufficient contrast enhancement (n=10), missing slice or trigger artefact (n=2), and 6 segments were excluded because of lack of information on conventional CA. After exclusion of stented segments, 9% of coronary artery segments were regarded as uninterpretable. Twenty-eight (11%) segments were excluded in the group with Agatston score 0-100, 16 (9%) in the group with Agatston score 101-400 and 3 (3%) in the group with Agatston score >400 (p=0.03). After exclusion of 43 stented segments and 13 coronary segments having insufficient image quality due to motion artefacts (n=3) or too small vessel size (n=10), 800 segments of 60 patients examined by 64-slice MSCT were included in the analysis. Having excluded stented segments, 2% of coronary artery segments were regarded as uninterpretable. No coronary segments were excluded in the group with Agatston score 0-100, while 8 (3%) were excluded in the group with Agatston score 101-400 and 5 (2%) in the group with Agatston score >400 (p=0.03).

The percentages of false positive and false negative segments in the groups with overall Agatston score 0-100, 101-400 and >400 in patients examined with 16- and 64-slice MSCT are given in Table 2. Only the difference between false negative segments in patients examined with 16-slice MSCT was found to be significant (0%, 5.3%, 2.9%, p=0.0005).

Table 2. Percentages of interpretable, false positive and false negative segments in the groups with different calcium scores

	Agatston score 0-100	Agatston score 101-400	Agatston score >400	p value
16 -slice Multi-slice Computed Tomography Coronary Angiography				
Interpretable, nr (%)	219/247 (89)	169/185 (91)	105/108 (97)	p=0.03
False positive, nr (%)	1/219 (0.5)	2/169 (1.2)	3/105 (2.9)	*p=0.1
False negative, nr (%)	0/219 (0)	9/169 (5.3)	3/105 (2.9)	*p=0.0005
64-slice Multi-slice Computed Tomography Coronary Angiography				
Interpretable, nr (%)	253/253 (100)	266/274 (97)	281/286 (98)	p=0.03
False positive, nr (%)	1/253 (0.4)	7/266 (2.6)	5/281 (1.8)	*p=0.07
False negative, nr (%)	4/253 (1.6)	5/266 (1.9)	7/281 (2.5)	*p=0.55

* the lowest p values of the comparisons between the groups.

Evaluation of impact of calcium on diagnostic accuracy of MSCT CA: vessel by vessel analysis

The results of per vessel analysis are provided in Table 3 and Figure 3. In the patient population examined with 16-slice MSCT, 5 vessels were regarded as uninterpretable due to >1 uninterpretable segment present in the coronary artery, resulting in 159 vessels included in the analysis. Conventional CA detected 33 (21%) coronary vessels with obstructive coronary lesions in the patient group examined with 16-slice MSCT CA, resulting in overall sensitivity of 76% and specificity of 97%. All 240 vessels were regarded as interpretable in patients examined with 64-slice MSCT. Fifty-seven (24%) vessels examined with 64-slice MSCT CA showed obstructive coronary stenoses and the calculated sensitivity and specificity were 79% and 96%, respectively. No significant differences of diagnostic accuracies of 16-, 64-slice and combined evaluation of 16- and 64-slice MSCT CA were noted between the groups of patients with Agatston scores in the range of 0-100, and >100 (Table 3 and Figure 3).

Table 3. Diagnostic accuracy of Multi-slice Computed Tomography Coronary Angiography in vessels with different calcium scores

	All vessels (n=159)	Agatston score 0-100 (n=120)	Agatston score >100 (n=39)
16-slice Multi-slice Computed Tomography Coronary Angiography			
Sensitivity, %	76 (61-91)	67 (43-91)	83 (66-100)
Specificity, %	97 (94-100)	99 (97-100)	86 (71-100)
Positive predictive value, %	86 (73-98)	91 (74-100)	83 (66-100)
Negative predictive value, %	94 (90-98)	95 (91-99)	86 (71-100)
	All vessels (n=240)	Agatston score 0 -100 (n=175)	Agatston score >100 (n=65)
64-slice Multi-slice Computed Tomography Coronary Angiography			
Sensitivity, %	79 (68-89)	77 (61-93)	81 (67-95)
Specificity, %	96 (93-99)	97 (94-100)	92 (85-98)
Positive predictive value, %	87 (78-96)	83 (68-98)	89 (77-100)
Negative predictive value, %	94 (91-97)	96 (93-99)	84 (72-96)

Values in parentheses represent 95% confidence intervals.

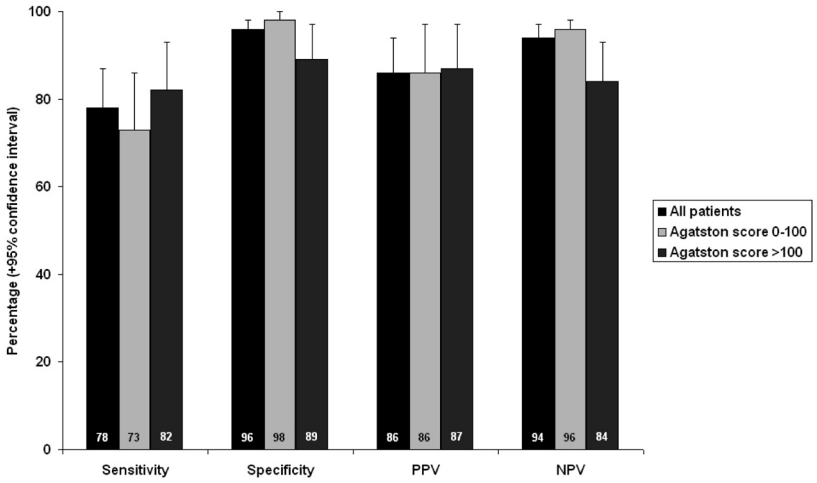

Figure 3. Diagnostic accuracies (per vessel analysis) and confidence intervals of 16- and 64-slice multi-slice computed tomography coronary angiography.
PPV, positive predictive value; NPV, negative predictive value.

Evaluation of impact of calcium on diagnostic accuracy of MSCT CA: patient by patient analysis

The diagnostic performance of MSCT CA for detecting obstructive lesions in patient groups with different overall Agatston scores on a patient-based analysis is detailed in Table 4 and Figure 4. In the patient group examined with 16-slice MSCT CA, obstructive coronary lesions were detected by conventional CA in 18 patients (44%), resulting in overall sensitivity of 89%, the specificity being 87%. Thirty-two patients (53%) examined with 64-slice MSCT CA had obstructive coronary stenoses, the calculated sensitivity was 91% and the specificity was 96%. As can be derived from Table 4 and Figure 4, no significant differences of diagnostic accuracies of 16-, 64-slice and combined evaluation of 16- and 64-slice MSCT CA were noted between the groups of patients having the Agatston scores in the range of 0-100, 101-400, >400 and >100.

Table 4. Diagnostic accuracy of Multi-slice Computed Tomography Coronary Angiography in patient groups with different calcium scores

	All patients (n=41)	Agatston score 0-100 (n=18)	Agatston score 101-400 (n=14)	Agatston score >400 (n=9)	Agatston score >100 (n=23)
16-slice Multi-slice Computed Tomography Coronary Angiography					
Sensitivity, %	89 (75-100)	100	75 (45-100)	100	86 (68-100)
Specificity, %	87 (73-100)	93 (80-100)	83 (53-100)	67 (29-100)	78 (51-100)
Positive predictive value, %	84 (68-100)	80 (45-100)	86 (60-100)	86 (60-100)	86 (68-100)
Negative predictive value, %	91 (79-100)	100	71 (37-100)	100	78 (51-100)
	All patients (n=60)	Agatston score 0-100 (n=19)	Agatston score 101-400 (n=20)	Agatston score >400 (n=21)	Agatston score >100 (n=41)
64-slice Multi-slice Computed Tomography Coronary Angiography					
Sensitivity, %	91 (81-100)	83 (53-100)	83 (62-100)	100	92 (82-100)
Specificity, %	96 (89-100)	100	88 (65-100)	100	93 (80-100)
Positive predictive value, %	97 (91-100)	100	91 (74-100)	100	96 (88-100)
Negative predictive value, %	90 (79-100)	93 (80-100)	78 (51-100)	100	88 (72-100)

Values in parentheses represent 95% confidence intervals.

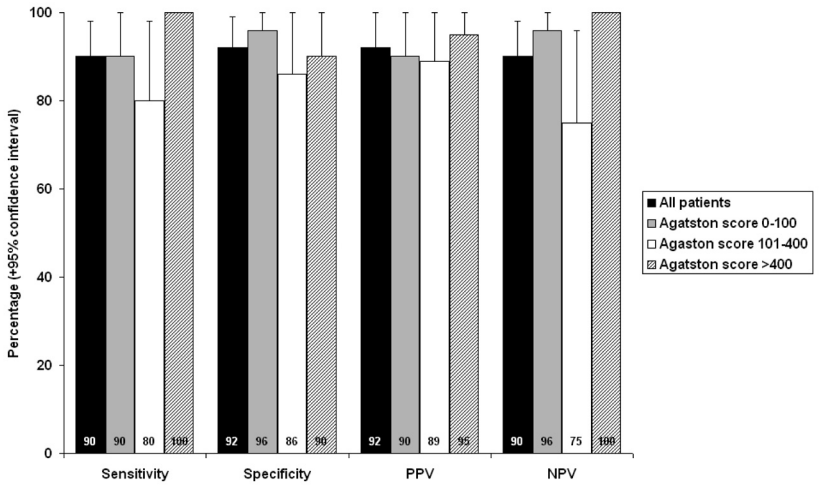

Figure 4. Diagnostic accuracies (per patient analysis) and confidence intervals of 16- and 64-slice multi-slice computed tomography coronary angiography.
PPV, positive predictive value; NPV, negative predictive value.

Discussion

The most important findings of the present study can be summarized as follows: (1) a negative impact of elevated coronary artery calcium score on diagnostic accuracy of MSCT CA was observed in the segment based analysis using 16-slice MSCT; this effect was not observed with 64-slice MSCT. Moreover, (2) elevated coronary artery calcium scores did not have a negative impact on the diagnostic accuracy of 16- and 64-slice MSCT CA when data were analyzed on vessel and patient basis.

In the current analysis, the accuracies of both the 16- and 64-slice MSCT to detect obstructive coronary artery disease were high, in line with previous publications.[3-5,10,11] In particular, the sensitivity and specificity of 16-slice MSCT were 89% and 87% for the detection of obstructive coronary artery stenoses, and pooled data from 11 studies with 681 patients using 16-slice MSCT revealed a sensitivity and specificity of 88% and 96% respectively.[2] The sensitivity and specificity of the 64-slice MSCT were higher being 91% and 96%. These values are in line with recently published data. For example, Mollet et al.[4] evaluated 52 patients with 64-slice MSCT and reported a sensitivity of 99% with a specificity of 95%. Of interest, the results of the current study confirm the high accuracies in populations with much higher prevalence of coronary artery disease as compared to the previous studies (being 44% for the patients undergoing 16-slice MSCT and 53% for the patients undergoing 64-slice MSCT).

In general, the sensitivity and specificity of 64-slice MSCT appear higher than of 16-slice MSCT. This may be related to improved image quality with 64-MSCT, which is reflected by the reduction in non-interpretable segments. Increased temporal and spatial resolution with 64-slice MSCT have led to a decrease in number of segments with impaired image quality, being 9% and 2% for 16- and 64-slice MSCT in the current study. These observations are in line with the literature; pooled analysis of 11 studies with 16-slice MSCT revealed that 4% (ranging between 0% to 17%) of segments were of uninterpretable image quality[2] as compared with all coronary segments included in the analysis in most 64-slice MSCT studies,[3,4] although one study reported exclusion of as high as 12% of segments.[11]

In addition, the reduced voxel size with 64-slice MSCT also positively influences partial volume effects of coronary calcifications. Coronary calcifications have high density and dominate the density of adjacent tissues in the same voxel. With reduction of voxel size, the blooming of calcium thus decreases. Indeed, the findings in the current study demonstrate the absence of influence of calcium score on the percentage of falsely diagnosed segments with 64-slice MSCT. A significant influence of the calcium score on

the percentage of false negative segments was however observed with 16-slice MSCT. These results are in line with previous observations, with 16-slice MSCT, that a significant number of coronary segments had to excluded from analysis due to severe calcifications.[9] Coronary calcifications were also demonstrated to be the major cause of false positive findings with 16-slice MSCT.[10]

Another important finding in the present study is that calcium score did not significantly impair the diagnostic accuracy of a vessel and a patient based analysis, both for 16- and 64-slice MSCT examinations. Although more false negative segments were observed in patients with higher calcium scores, indicating decreased sensitivity on a segmental basis, sensitivity increased when shifting to a patient level, most likely due to the higher prevalence of CAD in patients with higher calcium scores. These findings are particularly important in clinical practice as further diagnostic and therapeutic decisions are based on a patient based (rather than segment or vessel based) analysis in daily practice.

Limitations

Several limitations of the current study need to be acknowledged. The protocols used for 16- and 64-slice MSCT were not precisely identical; therefore it remains unknown to what extent small differences may have influenced our results in addition to the difference in collimation of the two scanner generations. Also, inclusion of patients examined with 16-slice MSCT scanner was limited, and may have influenced results. Finally, the effect of the presence of dense calcifications restricted to a small area (resulting in low overall calcium score), was not explored in the present study, while these calcifications may potentially also negatively influence diagnostic accuracy despite a low overall calcium score. Limitations of MSCT in general are that only qualitative analysis of severity of coronary stenoses with MSCT is feasible and more quantitative analysis techniques should be developed. Also, coronary MSCT remains limited by the high radiation exposure and the use of iodinated contrast.

Conclusions

In conclusion, the findings of the present study demonstrate that coronary calcium score only slightly affected the diagnostic accuracy of 16-slice MSCT on a segment based analysis and showed no statistically significant impact on vessel and patient basis. No significant impact of coronary calcium score was observed on the diagnostic accuracy of 64-slice MSCT CA on segment, vessel and patient basis.

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Chapter 5

Evaluation of Patients With Previous Coronary Stent Implantation With 64-Section CT

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Abstract

Aims: To prospectively evaluate the diagnostic accuracy of 64-section computed tomography (CT) for the assessment of in-stent or peri-stent restenosis, with conventional coronary angiography as the reference standard.

Methods: The study was approved by the medical ethics committee, and informed consent was obtained in all 50 enrolled patients (40 men, 10 women; mean age, 60 years±11 [standard deviation]). In addition to conventional coronary angiography with quantitative coronary angiography, 64-section CT was performed. For each stent, assessability was determined and was related to stent characteristics and heart rate by using a χ^2 test. On the interpretable images of stents and peri-stent lumina (5.00 mm proximal and distal to the stent), the presence of significant (≥50%) restenosis was determined. For this analysis, partially overlapping stents were considered to represent a single stent.

Results: Of 76 stents, 65 (86%) were determined to be assessable. Increased heart rate and overlapping positioning were associated with increased uninterpretability of the images of stents ($p<0.05$), whereas location of the stent and thickness of the strut were not. In seven patients, stents were placed in an overlapping manner, resulting in 58 stents available for the evaluation of significant (≥50%) in-stent restenosis. All six significant (≥50%) in-stent restenoses were detected, and the absence of significant (≥50%) restenosis was correctly identified in the 52 remaining stents, resulting in sensitivity and specificity of 100%. Sensitivity and specificity for the detection of significant (≥50%) peri-stent stenosis were 100% and 98%, respectively.

Conclusions: In selected patients with previous stent implantation, 64-section CT can be used to evaluate in-stent restenosis with high accuracy. Accordingly, the technique may be useful for noninvasive exclusion of in-stent or peri-stent restenosis, thereby avoiding invasive imaging in a considerable number of patients.

Introduction

Follow-up imaging in patients who present with recurrent symptoms after previous placement of an intracoronary stent is currently performed with conventional coronary angiography. However, this is an invasive procedure associated with a small but definite risk of serious complications.[1,2] Because a substantial number of procedures are not followed by an intervention, a noninvasive diagnostic procedure that helps evaluate not only native coronary arteries but also coronary stents would therefore be of great benefit. Although promising results have been obtained with multisection computed tomography (CT) for the detection of coronary artery stenoses in native coronary arteries,[3–5] results of evaluation of metallic stents have not been as promising.[6–10] Although image quality and diagnostic accuracy improved substantially with 16-section as compared with four-section CT systems, image quality for relatively large numbers of images of stents has been reported to be inadequate. In particular, images of stents with thicker struts or smaller diameters tended to exhibit degraded image quality.[6,7,9] Recently, 64-section CT systems have become available, and results of studies in which the in vitro assessment of coronary stents was evaluated by using 64-section CT suggest that further improvement in image quality has been achieved.[11,12] However, only limited data with 64-section CT are available in patients thus far, and results have been conflicting. Rixe et al,[13] for example, recently reported that only 58% of images of stents were interpretable.

Thus, the purpose of our study was to prospectively evaluate the diagnostic accuracy of 64-section CT for the assessment of in-stent or peri-stent restenosis, with conventional coronary angiography as the reference standard.

Methods

Patients

The study group consisted of 50 consecutive patients (40 men, 10 women; mean age, 60 years±11 [standard deviation]; range, 41–79 years) who met our criteria and who had previously undergone percutaneous transluminal coronary angioplasty in combination with stent placement. Characteristics of the study population are included in Table 1. Patients were scheduled for diagnostic conventional coronary angiography from June 2005 to May 2006. In addition, multisection CT coronary angiography was performed to allow noninvasive evaluation for the presence of in-stent restenosis or occlusion. Exclusion criteria were the following: (a) atrial fibrillation, (b) renal insufficiency (serum creatinine level >120 mmol/L), (c) known allergy to iodinated contrast media, and (d) pregnancy. All

patients were receiving continuous β-adrenergic blocking agent therapy, and no additional β-adrenergic blocking agents were administered prior to multisection CT. On average, multisection CT was performed a mean of 13.4 months±13.3 (range, 1–66 months) after stent implantation.

Conventional coronary angiography in combination with quantitative coronary angiography was performed 14 days±9 (mean±SD) after multisection CT and served as the reference standard. After the study details, including radiation exposure, were explained, all patients gave informed consent for our study that was approved by the ethics committee of the Leiden University Medical Center, Leiden, the Netherlands.

Table 1. Clinical characteristics of 50 patients in the study population

Characteristic	Value
Sex	
Men	40
Women	10
Age (y)*	60±11
Heart rate (beats/min)*	58±10
Single-vessel disease	22 (44)
Multivessel disease	28 (56)
Previous myocardial infarction	46 (92)
Anterior	31 (67)
Inferior	14 (30)
Both	1 (2)
Previous percutaneous transluminal coronary angioplasty	50 (100)
Previous coronary artery bypass graft	0
Stent location	
Left main coronary artery	0
Left anterior descending coronary artery	36 (47)
Left circumflex coronary artery	11 (14)
Right coronary artery	29 (38)

Except where otherwise indicated, data are numbers of patients, and numbers in parentheses are percentages.

* Data are the mean ± standard deviation.

Stent characteristics

The diameter of implanted stents ranged from 2.25 to 4.0 mm (mean, 3.4 mm ±0.3), and the length ranged from 8.0 to 33.0 mm (mean, 19.4 mm ±5.0). In total, 21 stents were positioned with partial overlap. Ten stent types were evaluated, and most were non–drug eluting stents (Vision, Guidant, Santa Clara, Calif [n=33]; Driver, Medtronic, Minneapolis,

Minn [n=3]; Ave S7, Medtronic [n=2]; Ave S670, Medtronic [n=1]; Orbus, Orbus Medical Technologies, Fort Lauderdale, Fla [n=2]; Tristar, Guidant [n=2]; Bx Velocity, Cordis, Miami Lakes, Fla [n=1]; and Liberte´, Boston Scientific, Natick, Mass [n=1]). In addition, 31 drug-eluting stents (Cypher, Cordis, Miami, Fla [n=30]; Achieve, Guidant [n=1]) were included. Of these stents, the Cypher, Bx Velocity, and Tristar stents were considered to have thick struts (≥140 μm).

Data acquisition

Multi-section CT

Multi-section CT was performed (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan), with 64 detector rows and a section thickness of 0.5 mm and a rotation time of 0.4, 0.45, or 0.5 seconds, depending on the heart rate. The tube current was 350 mA at 120 kV. Between 90 and 105 mL of nonionic contrast medium (Iomeron 400; Bracco, Milan, Italy) was administered into the antecubital vein with a CT injection system (Stellant; Medrad, Pittsburgh, Pa), depending on the total scanning time, and the flow rate was 5.0 mL/sec. Repetitive low-dose monitoring examinations (120 kV, 10 mA) were performed 5 seconds after the start of injection of contrast medium. After the preset contrast enhancement threshold level of baseline Hounsfield units plus 100 HU in the descending aorta was reached, multi-section CT was automatically initiated. After a 2-second delay, data acquisition was performed during an inspiratory breath hold of approximately 10 seconds; the electrocardiogram was recorded simultaneously to allow retrospective gating of the data.

For evaluation of the coronary arteries and intracoronary stents, data were reconstructed by using a segmented reconstruction algorithm at 75% of the R-R interval with a section thickness of 0.5 mm and a reconstruction interval of 0.3 mm. If motion artifacts were still present in this phase (as occurred in 23 patients), additional reconstruction was explored to obtain the reconstruction phase with the fewest motion artifacts. For this purpose, images were reconstructed at a single level throughout the R-R interval in 20-msec steps to obtain information on the individual patient's pattern of cardiac motion. On the basis of these images, the time point to reconstruct the entire data set was chosen. Also, in all patients, an additional data set was reconstructed in the most optimal phase or phases by using a sharper reconstruction kernel (Q04 instead of Q05-07) to improve stent image quality.[14] Multi-section CT was performed successfully in all patients. The mean heart rate during the acquisition was 58 beats per minute ±10 (range, 38–86 beats per minute).

Conventional coronary angiography

Conventional coronary angiography was performed according to standard techniques by two experienced operators, one with 10 years of experience and the other (M.J.S.) with 15 years of experience. Vascular access was obtained by using the femoral approach with the Seldinger technique and a 6-F catheter.

Data analysis

Multi-section CT

For each coronary artery, the data set containing no motion artifacts or the fewest motion artifacts was transferred to a dedicated workstation (Vitrea2; Vital Images, Plymouth, Minn) for postprocessing.

Coronary stents were evaluated on both the standard-kernel and the sharper kernel reformations by using predominantly the original transverse multi-section CT images; manually obtained curved multiplanar reformations were used for verification of findings. Three dimensional volume-rendered reformations were not used. In addition, the transverse images and curved multiplanar reformations were viewed in three different window and level settings: The setting with a window width of 1000 HU and a window level of 200 HU was used as a standard window level, and settings with a window level and window width of 1600 HU and 300 HU and 2500 HU and 900 HU, respectively, were used to improve stent appearance. Assessment was performed with consensus reading by two experienced observers (J.W.J. and J.D.S.). Both readers were blinded to the conventional coronary angiographic results, and both had 3.5 years of experience in the evaluation of findings at multi-section CT coronary angiography. One (J.W.J.) also had extensive (15 years) experience with conventional coronary angiography and intervention.

First, images of each stent were assigned an image quality score of 1 (good image quality, no artifacts), 2 (moderate image quality, minor or moderate artifacts present but diagnosis possible), or 3 (uninterpretable, no diagnosis possible), as described elsewhere.[9,15] Also, the reviewers documented whether stents were positioned in partially overlapping positions. Overlapping stents were consequently considered to represent a single stent for the evaluation of in-stent or peri-stent stenosis.

Subsequently, the presence of significant restenosis (≥50% reduction of luminal diameter) was assessed for each stent, and the observation of nonsignificant (≥50% reduction of luminal diameter) neointimal hyperplasia within the stent was documented. Finally, since re-stenosis of the stent borders may also regularly occur, the presence of persistent stenosis (≥50% narrowing of luminal diameter 5.00 mm proximal and distal to the stent) was also evaluated, as described elsewhere.[9]

Conventional and quantitative coronary angiography

Conventional angiograms were evaluated in consensus by two experienced observers (G.P., J.C.T.) who had no knowledge of the multi-section CT data. First, the location of the intracoronary stents was identified on the images before injection of contrast medium. Subsequently, quantitative coronary angiography with automated vessel contour detection after catheter-based image calibration was performed in end-diastolic frames by two qualified observers (G.P. and J.C.T.) who had 2 and 10 years of experience, respectively, in quantitative coronary angiography. The observers used a standard algorithm dedicated to stent analysis (QAngio XA, QCA-CMS, version 6.0; Medis, Leiden, the Netherlands).[16] Quantitative coronary angiography of the stent and its proximal and distal (5.00 mm) lumina was performed, and the percentage reduction in diameter was determined. An in-stent luminal diameter that was narrowed by 50% or more (up to in-stent occlusion) was defined as significant restenosis.

Statistical analysis

Continuous variables are presented as means ±1 standard deviation, and categorical data are summarized as frequencies and percentages. To relate stent assessability to stent characteristics, stents were classified according to the location in the coronary tree and according to strut thickness. Stents with struts that were 140 μm thick or thicker were regarded as having thick struts, and stents with struts that were less than 140 μm thick were regarded as having thin struts, as described elsewhere.[9] We also distinguished between stents positioned in partially overlapping positions and stents that were not overlapping. The percentage of assessable stents was calculated for each category and was compared by using χ^2 analysis, with Yates correction. In addition, mean heart rate was compared between patients with images of stents that were interpretable and patients with images of stents that were uninterpretable because of attenuation artifacts or motion artifacts; for this comparison, the Student *t* test for independent samples was used. Logistic regression analyses were applied to correlate segment and patient characteristics to image quality by using the generalized estimating equation method developed by Liang and Zeger.[17] Two (dichotomous) outcome variables were considered: (a) good versus moderate or uninterpretable image quality and (b) good or moderate versus uninterpretable image quality. The generalized estimating equation analysis was performed with Proc Genmod, with a binomial distribution for the outcome variable, with the link function specified as logit, and with patients considered as separate subjects.

Odds ratios and 95% confidence intervals were reported. Sensitivity, specificity, and positive and negative predictive values (including 95% confidence intervals) for the detection of in-stent restenosis of 50% or greater, as determined with conventional angiography in combination with quantitative coronary angiography, were determined for each stent. In addition, diagnostic accuracy was also determined for the detection of significant (≥50%) narrowing of the peri-stent lumina (5.00 mm proximal and distal to the stent).

Statistical analyses were performed with software (SPSS, version 12.0, SPSS, Chicago, Ill; SAS, release 6.12, SAS Institute, Cary, NC). A p value of .05 was considered to indicate a statistically significant difference.

Results

Stent analysis: image quality

In 50 patients, a total of 76 stents (one to five stents per patient; mean number of stents, 1.5±0.87) were evaluated (Figure 1). Quality of images of 41 (54%) stents was good and quality of images of 24 (32%) stents was moderate; the stent lumen could not be visualized on images of the remaining 11 (14%) stents. The reasons for uninterpretability of images of these 11 stents were motion artifacts on images of five (45%) stents and attenuation artifacts on images of six (55%) stents.

Of the images of stents that were uninterpretable, images of six stents that were placed in the right coronary artery were among them, whereas images of three stents that were positioned in the left anterior descending artery and images of two stents that were placed in the left circumflex coronary artery were included. No significant differences were observed in interpretability of images of stents placed among the coronary arteries (p=0.35). The mean heart rate during data acquisition was significantly higher in patients with images of stents deemed uninterpretable because of motion artifacts (mean, 72 beats per minute ±9) than in patients with images of stents deemed uninterpretable because of attenuation artifacts (mean, 55 beats per minute ±2) (p=0.002). No significant difference in heart rate was observed between images of stents that were uninterpretable because of attenuation artifacts and images of stents that were interpretable (mean, 57 beats per minute ±9; p=0.62).

Among images of stents positioned without any overlap (n=55), quality was good in 31 (56%), moderate in 20 (36%), and nondiagnostic in four (7%). In contrast, quality of images of stents positioned with partial overlap (n=21) was significantly lower — quality in these images of stents was good in 10 (48%) and moderate in four (19%), whereas images of seven (33%) stents were uninterpretable (p=0.01).

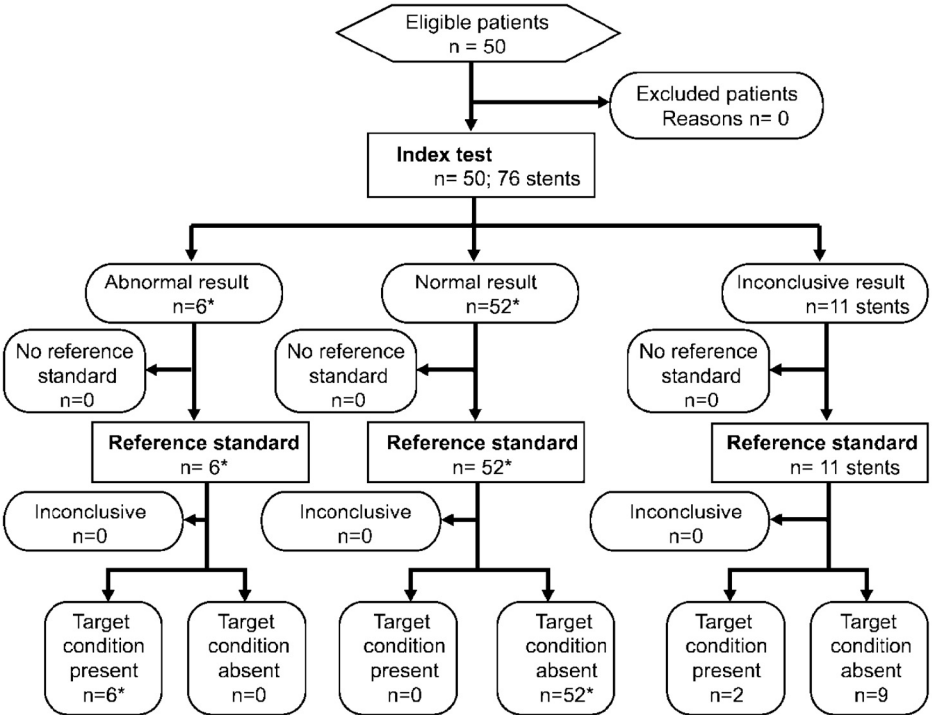

Figure 1. Flowchart.

* Total number of stents is lower than indicated in the boxes above because overlapping stents were considered to represent a single stent for the analysis of diagnostic accuracy.

A trend toward improved image quality for stents with thin struts (<140 μm thick, n=43) as compared with stents with thick struts (≥140 μm thick, n=33) could be observed. In the latter group, images of 14 (42%) stents were of good quality, those of 12 (36%) stents were of moderate quality, and images of seven (21%) stents were uninterpretable. In contrast, quality of images of 27 (63%) stents with thinner struts was good, and quality of images of 12 (28%) stents was moderate; images of four (9%) of the stents with thinner struts were uninterpretable. Still, no statistically significant difference was observed (p=0.15). Results from generalized estimating equation analysis are provided in Table 2.

Table 2. Results from generalized estimating equation analysis

Image quality	Odds ratio*
Good versus moderate or uninterpretable	
Heart rate†	0.98 (0.93, 1.05)
Overlapping stents (yes or no)	0.70 (0.17, 2.96)
Strut thickness (≥140 μm or <140 μm)	0.44 (0.15, 1.29)
Good or moderate versus uninterpretable	
Heart rate†	0.94 (0.86, 1.03)
Overlapping stents (yes or no)	0.16 (0.03, 0.87)
Strut thickness (≥140 μm or <140 μm)	0.38 (0.08, 1.77)

* Numbers in parentheses are the 95% confidence intervals.

† Odds ratio is expressed per beat per minute.

Stent analysis: diagnosis of significant in-stent restenosis

In seven patients, a total of 21 stents were placed in partially overlapping positions, thereby hampering individual evaluation of the presence of in-stent restenosis. Consequently, overlapping stents were considered as a single stent. As a result, 58 stents were available for the diagnosis of significant (≥50% reduction in luminal diameter) in-stent restenosis. Significant restenosis was correctly ruled out in all 52 stents that lacked significant in-stent restenosis, as determined with conventional coronary angiography in combination with quantitative coronary angiography (Figures 2, 3). The remaining six stents with significant in-stent restenosis were correctly identified at multi-section CT (Figure 4).

Table 3. Diagnostic accuracy for detection of significant in-stent or peri-stent restenosis

Statistic	≥50% In-stent restenosis	Peri-stent restenosis
Assessable stents*	65/76 (86)†	128/129 (99)‡
Sensitivity	6/6 (100)	5/5 (100)
Specificity	52/52 (100)	121/123 (98)§
Positive predictive value	6/6 (100)	5/7 (71)‖
Negative predictive value	52/52 (100)	121/121 (100)

Values are numbers of stents. Numbers in parentheses are percentages.

* Includes all available stents. For the calculation of diagnostic accuracy, partially overlapping positioned stents were considered as a single stent.

† The 95% confidence interval was 78% to 94%

‡ The 95% confidence interval was 97% to 100%,

§ The 95% confidence interval was 96% to 100%

‖ The 95% confidence interval was 37% to 100%.

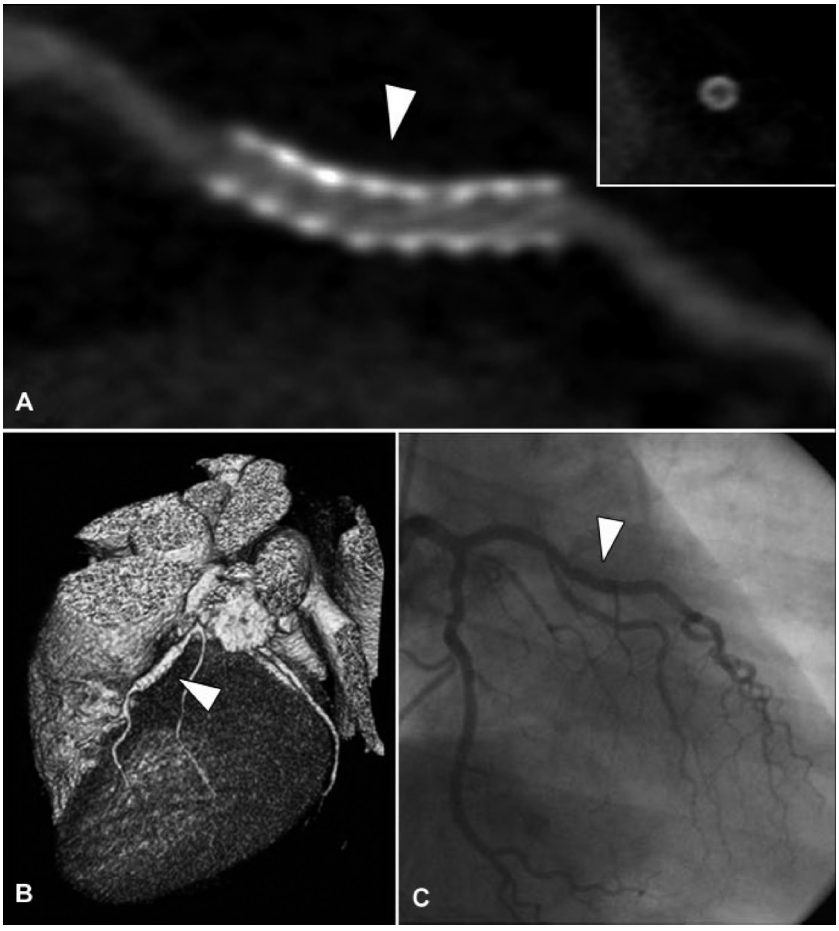

Figure 2. Patent thick-strut drug-eluting stent (diameter, 3.5 mm) placed in the left anterior descending coronary artery of a 53-year-old man. (A) Curved multiplanar and, (B) a three-dimensional volume-rendered reformation show the stent, with only limited neointimal hyperplasia (arrowhead, also on C). On the crosssectional image (inset on *A*), no significant in-stent restenosis was observed. (C) Corresponding conventional coronary angiogram.

Accordingly, the sensitivity and specificity for the assessment of significant in-stent restenosis were each 100% (Table 3). In the 52 stents without significant in-stent restenosis, the mean luminal narrowing as determined with quantitative coronary angiography was 23.4% ±8.6 (range, 4.3–42.4%). Nonsignificant restenosis could be observed at multi-section CT in 37 (71%) stents, whereas no neointimal hyperplasia could be observed at multi-section CT in 15 stents. In stents without neointimal hyperplasia visible at multi-section CT, the mean luminal narrowing as determined with quantitative coronary angiography was slightly but not substantially lower than that of stents with visible neointimal hyperplasia (20.6% ±11.7 versus 24.0% ±7.6).

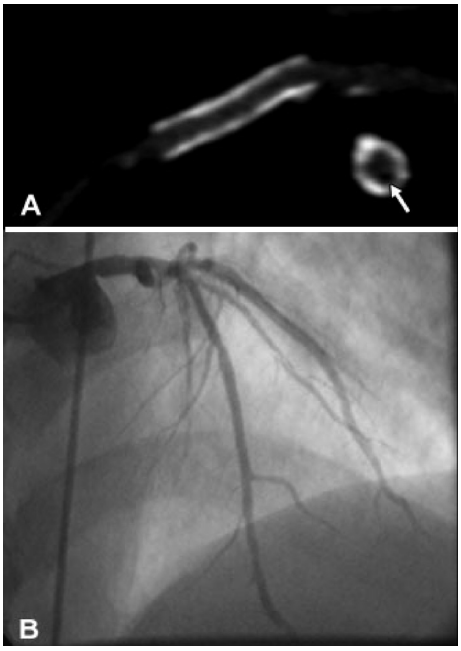

Figure 3. Patent thin-strut, non–drug-eluting stent (diameter, 3.5 mm) placed in the left anterior descending coronary artery of a 46-year-old man. (A) Curved multiplanar reformation shows the stent. At lower right-hand corner, cross-sectional image perpendicular to the stent helps confirm the presence of only minimal in-stent hyperplasia (appearing as a small rim of hypoattenuating tissue [arrow]). (B) Invasive coronary angiogram confirmed observations.

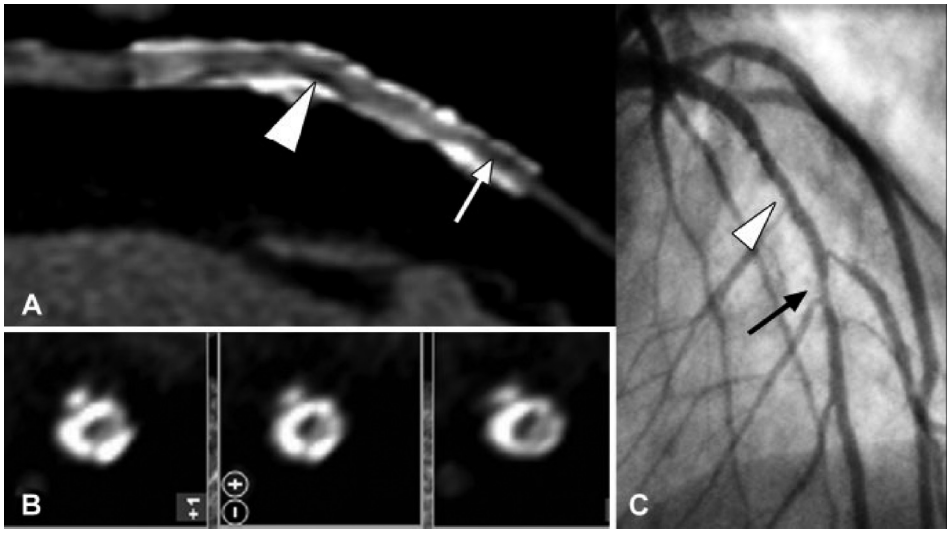

Figure 4: In-stent restenosis in two adjacent non– drug-eluting stents (diameters, 3.5 mm [proximal stent] and 3.0 mm [distal stent]) placed in the left anterior descending coronary artery of a 61-year-old man. (A) Curved multiplanar reformation shows in-stent restenosis (slightly exceeding 50% luminal diameter narrowing at the middle level (arrowhead, also on C) and more severe at the distal part of the stent (arrow, also on C)) in the two stents. (B) Three cross-sectional images obtained at the middle level show in-stent restenosis (appearing as hypoattenuating tissue). (C) Invasive coronary angiogram confirmed findings.

Peri-stent lumina

Of the 76 implanted stents, 21 were positioned in partially overlapping positions (Table 3). As a result, 55 single stents and 10 stents resulting from overlapping stents were available for evaluation. Also, one stent (located in the right coronary artery) originated directly from the aorta. Accordingly, 64 proximal stent lumina and 65 distal stent lumina were available for analysis. Images of all but one (1%) of the 129 peri-stent lumina were of sufficient quality to permit evaluation of the presence of significant narrowing. Conventional coronary angiography in combination with quantitative coronary angiography depicted the presence of significant stenosis in five peri-stent lumina. Stenoses in all five were correctly identified at multi-section CT. However, two lesions (one proximal and one distal) were overestimated with multi-section CT, resulting in a specificity of 98%.

Discussion

In our study, 76 coronary stents were evaluated by using 64-section CT, and 65 (86%) images of these stents were interpretable. Both elevated heart rate and overlapping positioning appeared to be associated with decreased interpretability, although no effect of stent type or location was observed. For the interpretable images of stents, sensitivity and specificity for detection of significant (≥50%) in-stent restenosis were each 100%, whereas the presence of nonobstructive in-stent restenosis was accurately identified in 71% of stents. In addition, the presence of peri-stent stenosis could be accurately detected, with a sensitivity and a specificity of 100% and 98%, respectively.

Our current observations compare favorably with those of previous studies of coronary stent imaging with 16-section CT. In an earlier study by Schuijf et al,[9] 21 patients with 65 previously implanted stents were evaluated. A moderate sensitivity of 78% and an excellent specificity of 100% for detection of in-stent restenosis were observed. However, only 50 (77%) stents were of sufficient image quality for evaluation. Exploration of the characteristics of images of 23% of the stents that were uninterpretable showed that predominantly images of stents with thicker struts (≥140 μm), as well as images of stents with smaller diameter (eg, ≤3.0 mm), tended to be affected by degraded image quality. The effect of thick struts was particularly pronounced; images of 41% of stents with thick struts were uninterpretable, as compared with images of 11% of stents with thinner struts. Diameter showed a less prominent effect; however, the percentage of images of stents that were uninterpretable was still substantially higher for those of stents with a diameter of 3.0 mm or less than it was for those of stents with a larger diameter (28% versus 11%). These

observations were recently confirmed in a larger population (143 patients with a total of 232 stents).[6] In this study by Gilard et al, who also used 16-section CT, a substantial increase in interpretability — from 51% to 81%—was observed for images of stents with diameters of greater than 3.0 mm as compared with images of stents with diameters of 3.0 mm or less. In addition, sensitivity for detection of in-stent restenosis increased similarly from 54% to 86%. For all stents, regardless of diameter, the specificity was 100%. In the study by Gilard et al, the researchers did not explore the effect of strut thickness.

In our study, improved interpretability of images of stents was observed with 64-section CT, and image quality was sufficient on images in 86% of stents. Exploration of the characteristics of images of stents that were uninterpretable showed that, as in previous studies, in native coronary arteries, an elevated heart rate was an important cause of nondiagnostic image quality.[18] Images of 45% of stents could not be interpreted because of motion artifacts. Accordingly, these observations underline the need for adequate control of heart rate during multi-section CT coronary angiography.

Findings of further evaluation of the uninterpretable images of stents indicated that partially overlapping stents are also associated with deteriorated image quality. The increased metal content is likely to amplify high-attenuation artifacts, thereby increasing the artificial narrowing of the lumen of the stent. Although images of 93% of single stents were interpretable, images of 33% of partially overlapping stents were of nondiagnostic quality. Accordingly, in patients with partially overlapping stents, evaluation by means of a modality other than multi-section CT may be preferred. In contrast to previous studies, no pronounced effect of strut thickness was observed. The presence of thick struts tended to result in nondiagnostic image quality more often than did the presence of thin struts (21% versus 9%; p=0.15). Accordingly, the influence of strut thickness on image quality with 64-section CT should be evaluated in a larger cohort because our study may have been underpowered to demonstrate any effect.

On the interpretable images of stents, the presence or absence of significant (≥50%) in-stent restenosis was correctly identified in all stents. Also, the presence or absence of peri-stent restenosis could be detected with a diagnostic accuracy of 98%. In particular, the observed negative predictive value to exclude the presence of in-stent or peri-stent restenosis was extremely high. Accordingly, the technique may be well suited to help noninvasively rule out significant (≥50%) in-stent or persistent restenosis. Somewhat lower sensitivity and specificity were reported in a recent study in which 40-section CT was used.[19] In that study by Gaspar et al in which 65 patients with 111 implanted coronary

stents were evaluated, the sensitivity and specificity for detection of 50% or greater in-stent restenosis were 89% and 81%, respectively.[19] In part, this discrepancy may be explained by the fact that Gaspar et al excluded only a small number (5%) of stents from the analysis, whereas we excluded a greater number. Still, a high negative predictive value (97%) was observed in the study by Gaspar et al, underlining the potential of multi-section CT as a noninvasive technique to rule out the presence of in-stent restenosis.

Another finding of our study was that, unlike the findings seen with 16-section CT,[9,14] the superior image quality of 64-section CT has improved visualization of nonsignificant in-stent hyperplasia in addition to significant in-stent restenosis. The presence of in-stent hyperplasia, albeit limited, was depicted with quantitative coronary angiography in all stents and was also correctly recognized in 71% of stents at multi-section CT. Our observations are agree with those of a recent study by Mahnken et al[20] in which 64-section CT was used in a phantom model. Comparison of 16-section CT with 64-section CT for imaging of eight 3.0-mm diameter stents positioned in a static chest phantom revealed superior visualization of stent lumina with 64-section CT because of significantly less artificial lumen reduction and image noise. Still, a considerable portion of stent lumina remained obscured even with 64-section CT; in our study, the presence of neointimal hyperplasia could not be observed at multi-section CT in 30% of stents. Accordingly, the value of multi-section CT to identify moderate in-stent hyperplasia appears to remain limited at present.

Our study does have some limitations. First, we evaluated a relatively small number of patients. As a result, the total number of stents and the number of patients with significant in-stent restenosis (12%) were relatively low as well. Nonetheless, a much higher prevalence of in-stent restenosis is not likely to be encountered in daily practice, and extrapolation of the current results to clinical practice may therefore be justifiable.[21,22] Second, the number of evaluated stents was low and the influence of stent and patient characteristics on interpretability of images of stents should be explored in larger patient cohorts to fully establish which characteristics should potentially be avoided in the evaluation of stents with multi-section CT. In particular, the range of stent diameters was limited in our study (mean, 3.4 mm ±0.3); as a result, we could not evaluate a potential effect of stent diameter. Thus, our study might best be regarded as a basis for further larger studies of image quality and diagnostic accuracy of 64-section CT in coronary stents. Third, despite the technologic advancements of 64-section CT, several limitations inherent to the technique remain. For example, as also observed in our study, a stable and low heart rate remains crucial for high-quality multi-section CT images, and administration of β-adrenergic blocking agents

prior to the examination is therefore often required.[18] Another limitation of multi-section coronary angiography is the patients' exposure to a relatively high effective radiation dose (10–15 mSv). For this reason, dose-modulation protocols are currently in development.

In conclusion, in selected patients with previous stent implantation, the sensitivity and specificity of 64-section CT were 100% each for detection of significant (≥50%) in-stent restenosis and 100% and 98%, respectively, for detection of significant (≥50%) persistent stenosis. In particular, 64-section CT may be useful for noninvasive exclusion of in-stent or peri-stent restenosis and for avoidance of invasive imaging in a considerable number of patients.

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Chapter 6

Head-to-Head Comparison Between Bicycle Exercise Testing and Coronary Calcium Score and Coronary Stenoses on Multi-Slice Computed Tomography

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Submitted

Abstract

Aims: To perform a head-to-head comparison between signs of ischemia during bicycle exercise testing and coronary atherosclerosis on multi-slice computed tomography (MSCT) in patients with suspected coronary artery disease (CAD).

Methods: 201 patients underwent exercise testing, followed by 64-slice MSCT. A subgroup of 63 (31%) patients also underwent conventional coronary angiography. The exercise test was positive or negative based on electrocardiographic signs of ischemia. On MSCT, total calcium score was obtained. Based on MSCT angiography, the patients were classified as having normal MSCT or coronary atherosclerosis (with non-obstructive and obstructive CAD (≥50% luminal narrowing) present).

Results: In 178 patients with interpretable examinations, the exercise test was positive in 36 (20%) and negative in 142 (80%) patients. Calcium score was identical in patients with a positive (11 (0-343)) and a negative exercise test (18 (0-335), p=NS). The prevalence of non-obstructive CAD was the same in 2 patients groups (13 (36%) patients with a positive versus 54 (38%) patients with a negative exercise test, p=NS). Although obstructive CAD was observed in 15 (42%) patients having a positive exercise test, obstructive lesions were also present in 38 (27%) patients without ischemia on exercise testing. The findings were confirmed by conventional coronary angiography.

Conclusion: No correlation was observed between ischemia on exercise testing and both calcium scoring and non-obstructive CAD on MSCT. A large proportion of obstructive lesions on MSCT were not demonstrated on exercise testing. Potentially MSCT may provide additional information on CAD.

Introduction

For the initial evaluation of the presence of coronary artery disease (CAD) non-invasive testing modalities are typically used. Frequently, exercise testing is used as a first-line examination as it is robust, widely available, relatively safe and inexpensive.[1] The test provides an estimate of the presence of myocardial ischemia. Nevertheless, an important limitation of exercise testing is its limited diagnostic accuracy to detect obstructive CAD.[2] In addition, while a positive test result is associated with adverse outcome, the prognostic value of a negative exercise test is less well established.[1,2]

Multi-slice computed tomography (MSCT) has recently been introduced as a novel imaging modality allowing direct non-invasive assessment of coronary atherosclerosis. Since a high diagnostic accuracy to detect or exclude obstructive lesions has been demonstrated,[3] the technique has been suggested as a potential non-invasive modality to establish or rule out the presence of obstructive CAD. In addition, MSCT allows quantitative assessment of coronary calcium and visualization of coronary plaques.[3,4] Preliminary studies reporting on the prognostic value of MSCT have demonstrated that MSCT has an independent prognostic value over baseline patient characteristics.[5,6]

Since both exercise testing and MSCT may be used for detection of CAD and provide different type of information (functional versus anatomical), it is important to understand how these modalities correlate. Indeed, previous studies demonstrated superior diagnostic accuracy of MSCT in detecting obstructive CAD as compared with exercise testing.[7,8] Nevertheless, more detailed information on the correlation between both a positive and a negative exercise test result and the anatomical observations of CAD on MSCT is still lacking. Accordingly, the purpose of the study was to assess the relationship between exercise testing results and the presence of coronary atherosclerosis on MSCT in patients with suspected CAD.

Methods

Patients and study protocol

A total of 201 patients were initially included in the study who underwent bicycle exercise testing and MSCT for the evaluation of CAD. The 2 examinations were performed within a time interval of 4 weeks; patients who developed acute coronary events or worsening of angina between the 2 examinations were excluded. A subset of patients (63 (31%)) also underwent conventional coronary angiography within 4 weeks after MSCT coronary angiography; referral was at the discretion of a treating physician based on clinical symptoms and the presence of CAD risk factors. Only patients without contraindications to MSCT [9] or exercise testing [2] were included. Informed consent was obtained in all patients.

Exercise testing

Exercise testing was performed on a bicycle ergometer according to the standard protocols.[10] The tests were analyzed by an experienced reader who was unaware of the results of MSCT and were classified as positive or negative for ischemia. The exercise test was considered positive based on the presence of ≥0.1 mV horizontal or downsloping ST-segment depression on the electrocardiogram (ECG) at 80 milliseconds after the J point in 2 contiguous leads during exercise or recovery.[2] The exercise test was considered uninterpretable if the patient failed to attain at least 85% of the age-predicted maximum heart rate with the absence of ischemic changes, if the ECG recording artifacts were observed during testing or if ECG changes were equivocal.[2]

MSCT

The examinations were performed using Toshiba Multi-slice Aquilion System (Toshiba Medical Systems, Tokyo, Japan). Patients underwent a prospectively triggered coronary calcium scan without contrast enhancement first, followed by 64-slice MSCT coronary angiography.[11]

First, total Agatston calcium score was recorded for all patients while coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU. Based on the total coronary calcium score, the patients were classified as having no or minimal coronary calcification (total calcium score <10) or extensive calcification (total calcium score >400). Subsequently, MSCT angiograms were evaluated in consensus by 2 experienced observers. All coronary angiograms were evaluated for interpretability and patients were excluded from the analysis in case of 1. an uninterpretable proximal or mid coronary segment or 2. more than 3 uninterpretable segments in general. The presence of coronary plaques was visually evaluated using axial images and curved multiplanar reconstructions. If present, plaques were classified as non-obstructive and obstructive using a 50% threshold of luminal narrowing. The patients were first classified as A) having a normal MSCT (no plaques visible) or as B) having coronary atherosclerosis (at least 1 coronary plaque detectable). In case of the presence of atherosclerosis, the patients were further classified as follows: 1) patients with non-obstructive CAD*,* if exclusively non-obstructive plaques were present, 2) patients with obstructive CAD*,* if at least 1 obstructive plaque was present, 3) patients with left main and/or 3-vessel CAD*,* if obstructive plaques were located in left main coronary artery and/or in all 3 vessels.

Conventional coronary angiography

Conventional invasive coronary angiography was performed according to standard protocols.[12] Coronary angiograms were evaluated by an experienced observer blinded to the study results. Coronary segments were classified using a modified 17 segment American Heart Association classification.[13] The presence of an obstructive lesion was defined as ≥50% luminal narrowing. Accordingly, the patients were evaluated for the presence or absence of obstructive CAD *(*at least 1 obstructive lesion was present) and, if present, further classified as having left main and/or 3-vessel CAD (in case of an obstructive lesion located in the left main coronary artery and/or all 3 vessels).

Statistical analysis

Categorical variables are expressed as numbers (percentages) and compared between groups with 2-tailed Chi-square test. Continuous variables are expressed as mean (standard deviation). When not normally distributed, continuous variables are expressed as medians (interquartile range) and compared between groups with 2-tailed non-parametric Mann-Whitney test.

P-values of <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS software (version 14.0, SPSS Inc, Chicago, Ill, USA).

Results

Patient population

A total of 201 patients were initially enrolled. The clinical characteristics of the patients at the time of inclusion in the study are presented in Table 1. MSCT was performed successfully in all but 2 (1%) patients, who had an elevated heart rate during the scan rendering the examination uninterpretable. In 21 (10%) patients, the exercise test was deemed uninterpretable: 12 patients did not reach 85% of the maximum predicted heart rate, ECG recording artifacts during exercise testing were observed in 2 patients and 7 patients developed equivocal ECG changes during exercise testing.

Table 1 Characteristics of the study population

	n=201
CAD risk factors	
Age (yrs, mean±SD)	56±11
Male gender	100 (50%)
Type 2 diabetes	28 (14%)
Hypercholesterolemia	121 (60%)
Hypertension	98 (49%)
Family history of CAD	100 (50%)
Smoking	67 (33%)
Body mass index (kg/m^2)	26±4
Obesity	65 (32%)
Previous history of CAD	
Previous PCI	22 (11%)
Previous MI	21 (10%)
Medications	
Use of ACEI/ARB	68 (34%)
Use of β-blockers	78 (39%)
Use of nitrates	23 (11%)
Use of statins	79 (39%)
Use of aspirin	75 (37%)

Data are absolute numbers (%), unless otherwise indicated.

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Exercise testing, MSCT and conventional coronary angiography findings

The exercise test was positive in 36 (20%) of 178 patients with interpretable results, whereas the test was negative in 142 (80%) patients.

The coronary calcium score was available in 177 (99%) patients (35 (20%) with a positive exercise test and 142 (80%) with a negative exercise test). The median coronary calcium score per patient was 18 (0-338). Minimal coronary calcifications (total calcium score <10) were observed in 81 (46%) patients, whereas extensive coronary calcifications (total calcium score >400) were detected in 37 (21%) patients.

On MSCT coronary angiography, 58 (32%) patients were classified as normal, whereas 120 (68%) patients had atherosclerosis. Non-obstructive CAD was observed in 67 (38%) patients, whereas obstructive CAD was present in 53 (30%) patients, 12 (23%) of these patients having left main and/or 3-vessel CAD.

A subset of 63 (35%) patients underwent conventional invasive coronary angiography. In total, obstructive CAD was detected in 35 (56%) patients, 11 (31%) of these patients having left main and/or 3-vessel CAD.

Exercise testing versus coronary calcium score

The total calcium score was identical among patients with a positive and a negative exercise test (Figure 1). The median calcium score in patients with a positive exercise test was 11 (0-343), whereas the median calcium score in patients with a negative exercise test was 18 (0-335) (p=NS). Minimal coronary calcification (total calcium score <10) was observed in 18 (51%) patients with a positive exercise test and in 63 (44%) patients with a negative exercise test (p=NS). Vice versa, extensive coronary calcification (total calcium score >400) was observed in 7 (20%) patients with a positive exercise test and in 30 (21%) patients with a negative exercise test (p=NS).

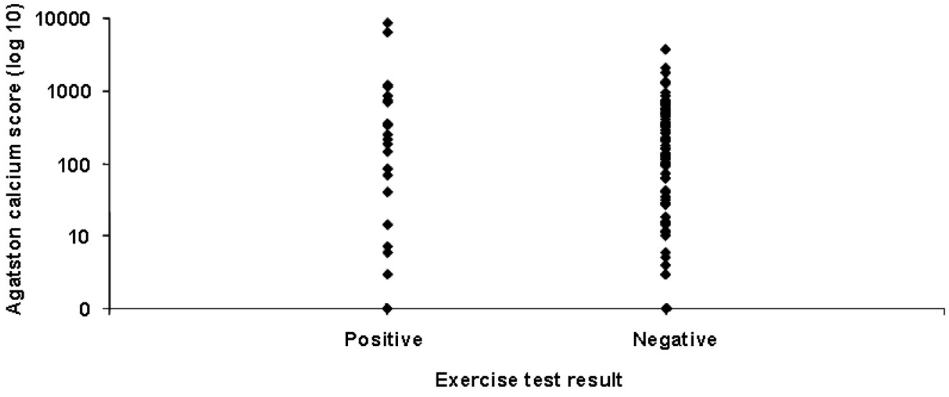

Figure 1. The results of exercise testing versus total Agatston calcium score on MSCT. Identical calcium scores were observed in patients with a positive and a negative exercise test.

Exercise testing versus stenoses on MSCT

The comparison between the findings on exercise testing and MSCT are presented in Figure 2. In patients with a positive exercise test, coronary atherosclerosis on MSCT was observed in 28 (78%) patients. Obstructive CAD was present in 15 (42%) patients (of which 5 (33%) had left main and/or 3-vessel CAD). Non-obstructive CAD was detected in 13 (36%) patients. In 8 (22%) patients with a positive exercise test, a normal MSCT was observed (no plaques visible).

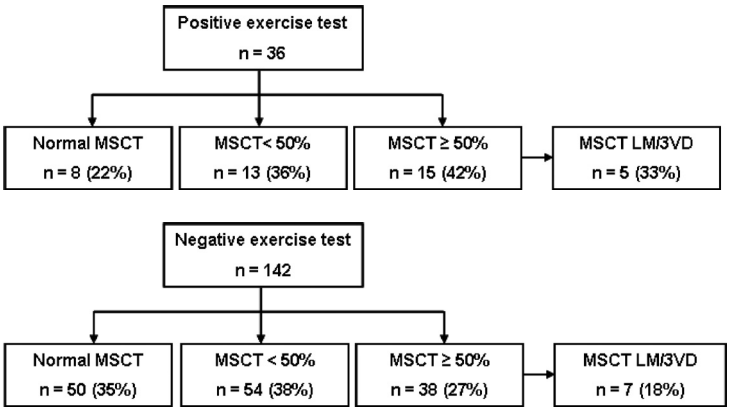

Figure 2. Relationship between the findings on exercise testing and MSCT.
Normal MSCT indicates the absence of any coronary plaques; MSCT <50% indicates the presence of exclusively non-obstructive CAD; MSCT ≥50% indicates the presence of obstructive CAD; MSCT LM/3VD indicates the presence of obstructive CAD in the left main coronary artery and/or all 3 coronary vessels.
CAD, coronary artery disease; LM, left main coronary artery; 3VD, 3-vessel disease.

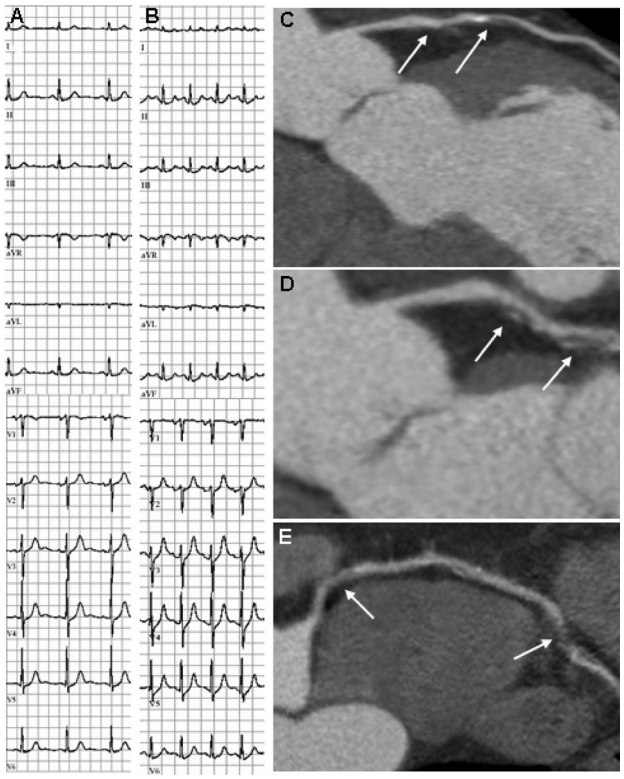

Figure 3. An example of a patient with 3-vessel coronary artery disease on MSCT and a negative exercise test. No signs of ischemia were observed on the electrocardiogram either at rest (A) or during maximal exercise (B). On MSCT, obstructive lesions were demonstrated in proximal left anterior descending coronary artery (arrows) (C), proximal left circumflex coronary artery (arrows) (D) and proximal and distal right coronary artery (arrows) (E).

In patients with a negative exercise test, a normal MSCT was obtained in 50 (35%) patients. Nevertheless, coronary atherosclerosis was identified in 92 (65%) patients. In these patients, non-obstructive CAD was observed in 54 (38%). Obstructive CAD was present in 38 (27%) patients, in which MSCT identified left main and/or 3-vessel CAD in 7 (18%). An example of a patient with 3-vessel CAD on MSCT coronary angiography despite a negative exercise test is provided in Figure 3.

Comparison of exercise testing and stenoses on MSCT to conventional coronary angiography

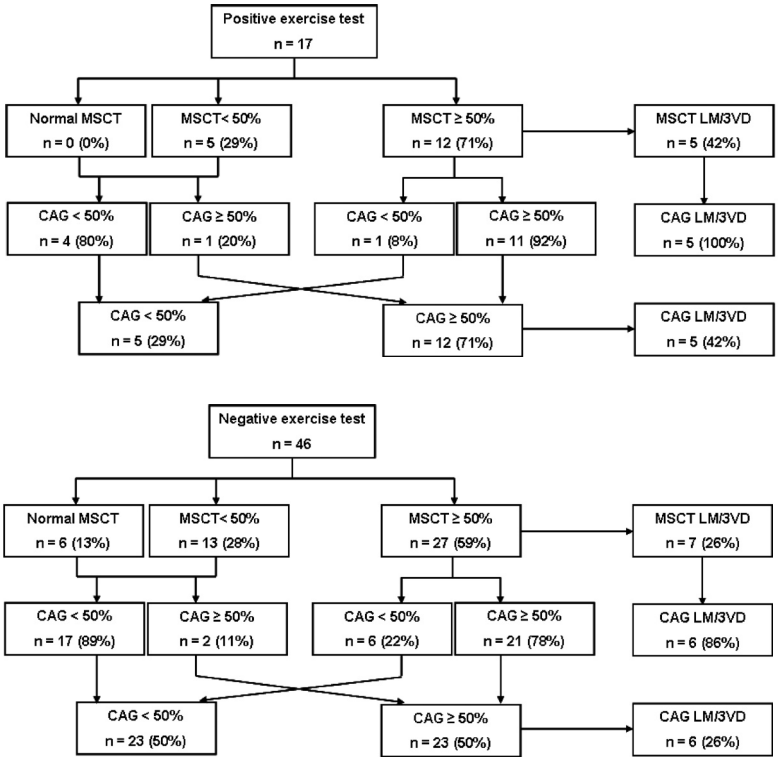

Figure 4. Relationship between the findings on exercise testing, MSCT and conventional coronary angiography.
Normal MSCT indicates the absence of any coronary plaques; MSCT <50% indicates the presence of exclusively non-obstructive CAD; MSCT ≥50% indicates the presence of obstructive CAD; MSCT LM/3VD indicates the presence of obstructive CAD in the left main coronary artery and/or all 3 coronary vessels.
CAG <50% indicates the absence of obstructive CAD; CAG ≥50% indicates the presence of obstructive CAD; CAG LM/3VD indicates the presence of obstructive CAD in the left main coronary artery and/or all 3 coronary vessels.
CAD, coronary artery disease; CAG, conventional coronary angiography; LM, left main coronary artery; 3VD, 3-vessel disease.

The comparison between the findings on exercise testing, MSCT coronary angiography and conventional invasive coronary angiography is provided in Figure 4. The majority of patients with a positive exercise test had obstructive CAD on conventional coronary angiography (12 (71%)). All but 1 patient with obstructive lesions were correctly identified by MSCT (11 of 12 (92%)). However, absence of obstructive CAD was still observed in 5 (29%) patients with a positive exercise test.

Concerning patients with a negative exercise test, obstructive CAD was absent on conventional coronary angiography in 23 (50%) of patients. All but 2 patients without obstructive lesions were correctly identified on MSCT (17 of 19 (89%)). Nevertheless, the exercise test was false negative in 23 (50%) patients and 6 (26%) of these patients had left main and/or 3-vessel CAD confirmed by conventional coronary angiography.

Uninterpretable exercise test versus MSCT coronary angiography

In 21 patients with an uninterpretable exercise test, obstructive CAD was observed in 6 (29%) patients. Four (67%) of these patients had left main and/or 3-vessel CAD. Non-obstructive CAD was identified in 10 (47%) patients, whereas a normal MSCT was observed in 5 (24%) patients.

Discussion

The findings of the study may be summarized as follows. Exercise testing and MSCT, which are frequently used for the primary evaluation of CAD, provide discrepant information. First, no evident relationship between the results of exercise testing and the presence of coronary calcium and non-obstructive atherosclerosis was observed. Second, although obstructive CAD was observed in a large proportion of patients with a positive exercise test, obstructive CAD was also detected in nearly one third of patients with a negative exercise test. Moreover, MSCT even identified a small but not negligible proportion of patients with left main and/or 3-vessel CAD despite the absence of ischemia on exercise testing.

Exercise testing versus coronary atherosclerosis

The present study failed to demonstrate an evident relationship between the presence of coronary atherosclerosis as determined on calcium scoring and MSCT angiography and results from exercise testing. Indeed, the median calcium score in patients with a positive exercise test result was comparable to the median calcium score in patients with a negative exercise test. At first sight, this observation contradicts previous observations comparing calcium scoring to myocardial perfusion imaging (MPI). In a large investigation including asymptomatic

individuals, a significantly higher mean coronary calcium score of 1,175 was observed in the 76 patients exhibiting abnormal MPI versus an average of 389 in the remaining 1,119 patients with normal MPI studies.[14] In symptomatic patients,[15] higher mean coronary calcium scores have been observed in patients with abnormal MPI as compared to patients with no perfusion abnormalities as well. Nonetheless, in these studies functional imaging still failed to identify substantial atherosclerosis in a considerable proportion of patients. In the study by Berman et al, extensive calcifications (total calcium scores >400) were observed in 31% of normal MPI studies.[14] Similarly, in the present study, calcium scores of >400 were identified in 21% of patients without signs of ischemia on exercise testing. Moreover, the prevalence of atherosclerosis was only slightly higher in patients with abnormal exercise tests (78%) with still a substantial proportion of patients (65%) without signs of ischemia on exercise testing having atherosclerosis. Nevertheless, the ability of MSCT to detect both obstructive and non-obstructive lesions may be of clinical importance since it has been demonstrated that myocardial infarction frequently occurs due to rupture of previously non-obstructive lesions.[16-19] Accordingly, MSCT may provide additional information on the presence of atherosclerosis.

Exercise testing versus obstructive stenosis

In accordance with previous studies comparing MSCT to exercise testing, a larger proportion of patients with obstructive CAD was observed in patients having detectable ischemia on exercise testing. Indeed, obstructive lesions were demonstrated in 42% of patients with a positive exercise test result. Nevertheless, obstructive lesions were also observed in 27% of patients with a negative exercise test. This is in line with observations by Rubinshtein et al [20] who compared exercise testing in 100 patients with a negative or non-diagnostic exercise test. The authors reported a prevalence of obstructive lesions in 22% of patients with a negative exercise test result. Importantly, in our study MSCT revealed left main and/or 3-vessel CAD in 5% of patients with a negative exercise test result, comparable to the study by Rubinshtein et al.[20] These observations were confirmed in a subgroup of patients who underwent conventional invasive coronary angiography.

On the contrary, although the absence of flow limiting lesions was correctly detected in 73% of patients having a negative exercise test, as many as 58% of patients without obstructive lesions on MSCT (and 22% patients with completely normal MSCT) were observed to have ischemia on exercise testing. Indeed, it is well known, that results from exercise testing may be influenced by a variety of clinical conditions such as the presence of arterial hypertension or previous CAD as well as female gender.[2] In contrast, these conditions appear to have no significant influence on the diagnostic accuracy of MSCT coronary angiography.[21,22]

Importantly, the presence of obstructive CAD could be excluded by MSCT in the majority of patients with an uninterpretable exercise test result. Accordingly, MSCT could possibly also provide valuable information in patients with an uninterpretable exercise test as previously suggested.[7]

Clinical implications

The study demonstrated that exercise testing and MSCT provide discrepant information on CAD. While exercise testing provides a general estimate on the presence of myocardial ischemia, MSCT provides more detailed information on coronary atherosclerosis including the presence and location of both obstructive and non-obstructive plaques. Accordingly, MSCT may possibly become an important component in the primary diagnostic work-up of patients with suspected CAD. In particular, MSCT would be a valuable evaluation tool in patients either with previous inconclusive exercise test results or unable to exercise. In addition, exercise testing may be less accurate in detecting obstructive CAD in general. Accordingly, depending on the likelihood of the presence of CAD, MSCT coronary angiography could be used in conjunction with exercise testing. Nevertheless, to develop and support such diagnostic algorithms, comparative data on clinical utility of MSCT and exercise testing in large patient populations and including follow-up are highly needed.

Limitations

The observations of the study are based on a relatively small patient population. Moreover, only a limited number of patients also underwent conventional coronary angiography. In this subset of patients, referral bias may have influenced observations. Limitations of MSCT include the fact that the technique is still associated with an elevated X-ray dose, while also the administration of contrast material is required. However, dose reduction is currently a topic of extensive investigation and recent investigations have demonstrated the feasibility of low-dose protocols without loss in image quality.[23,24]

Conclusions

Exercise testing and MSCT are frequently used for the primary evaluation of CAD but provide discrepant information. Moreover, MSCT identified a small but not negligible proportion of patients with extensive obstructive coronary lesions despite a normal exercise test. Future larger studies should demonstrate whether the use of exercise testing in conjunction with MSCT may provide more accurate information for optimal patient management.

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Part **II**

Prognosis and Coronary Plaque Imaging

Chapter 7

Prognostic Value of Multi-Slice Computed Tomography Coronary Angiography in Patients With Known or Suspected Coronary Artery Disease

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Abstract

Aims: This study sought to determine the prognostic value of multi-slice computed tomography (MSCT) coronary angiography in patients with known or suspected coronary artery disease (CAD).

Background: It is expected that MSCT will be used increasingly as an alternative imaging modality in the diagnosis of patients with suspected CAD. Data on the prognostic value of MSCT, however, are currently not available.

Methods: A total of 100 patients (73 men, age 59±12 years) who were referred for further cardiac evaluation due to suspicion of significant CAD underwent additional MSCT coronary angiography to evaluate the presence and severity of CAD. Patients were followed up for the occurrence of: 1) cardiac death, 2) nonfatal myocardial infarction, 3) unstable angina requiring hospitalization, and 4) revascularization.

Results: Coronary plaques were detected in 80 (80%) patients. During a mean follow-up of 16 months, 33 events occurred in 26 patients. In patients with normal coronary arteries on MSCT, the first-year event rate was 0% versus 30% in patients with any evidence of CAD on MSCT. The observed event rate was highest in the presence of obstructive lesions (63%) and when obstructive lesions were located in the left main (LM)/left anterior descending (LAD) coronary arteries (77%). Nonetheless, an elevated event rate was also observed in patients with nonobstructive CAD (8%). In multivariate analysis, significant predictors of events were the presence of CAD, obstructive CAD, obstructive CAD in LM/LAD, number of segments with plaques, number of segments with obstructive plaques, and number of segments with mixed plaques.

Conclusions: Multi-slice computed tomography coronary angiography provides independent prognostic information over baseline clinical risk factors in patients with known and suspected CAD. An excellent prognosis was noted in patients with a normal MSCT.

Introduction

In patients presenting with suspected or known coronary artery disease (CAD), assessment of prognosis is essential in selecting appropriate patient management. Currently, extensive data are available on the prognostic value of myocardial perfusion imaging with single-photon emission computed tomography (SPECT). A normal SPECT study has been shown to indicate a good clinical outcome with an annual death or infarct rate of <1% per year, whereas the likelihood to develop cardiac events is significantly increased when perfusion abnormalities are detected.[1,2] Similarly, coronary artery calcium score assessed by electron beam computed tomography (EBCT) or, less frequently, by multi-slice computed tomography (MSCT), has been used for risk stratification in patients with known or suspected CAD, and a calcium score <100 has been associated with excellent outcome, with an increase in the event rate paralleling the increase in calcium score.[3,4] More recently, noninvasive coronary angiography techniques (magnetic resonance imaging, EBCT, and MSCT) have been introduced which allow direct visualization of coronary artery lesions. At present, MSCT appears to be the most robust technique for this purpose, and it is expected that this technique will be increasingly used as an alternative first-line imaging modality in the diagnosis of patients presenting with chest pain suspect for CAD. Multi-slice computed tomography allows detection of both obstructive and nonobstructive lesions, and noncalcified lesions are also visualized. Although the diagnostic accuracy of MSCT has been demonstrated, data on the prognostic value of MSCT are not available. Accordingly, the aim of this study was to determine the prognostic value of MSCT in patients with known or suspected CAD.

Methods

Patients and study protocol

The study population consisted of consecutive patients who presented to the outpatient clinic and were referred for further evaluation (using exercise electrocardiogram, perfusion imaging, or invasive coronary angiography) of suspected CAD (chest pain complaints, elevated risk profile, or abnormal test results). In all patients, MSCT coronary angiography was performed in addition to the standard clinical workup. Subsequent clinical management was based on the latter; MSCT findings were not included in the diagnostic/therapeutic workup.

Only patients without previous coronary bypass grafting who were in sinus rhythm and without contraindications to iodinated contrast media were included, resulting in the exclusion of 5 patients because of potential contrast allergy (n=3) and atrial fibrillation (n=2), respectively. Follow-up was successful in all patients. All patients gave written informed consent to the study protocol, which was approved by the local ethics committee.

A structured interview and clinical history were acquired, and the following cardiac risk factors were assessed before the MSCT examination: 1) diabetes mellitus (defined as a fasting glucose level of ≥7 mmol/l or the need for insulin or oral hypoglycemic agents);[5] 2) hypercholesterolemia (defined as a total cholesterol level ≥5 mmol/l or treatment with lipid-lowering drugs);[6] 3) hypertension (defined as blood pressure ≥140/90 mm Hg or the use of antihypertensive medication);[7] 4) obesity (body mass index ≥30 kg/m^2);[8] 5) positive family history of CAD (defined as the presence of CAD in first-degree relatives younger than 55 [male] or 65 [female] years of age);[9] and 6) smoking (defined as previous or current smoking).

MSCT data acquisition

All examinations were performed using Toshiba Multi-slice Aquilion systems (Toshiba Medical Systems, Tokyo, Japan). If the heart rate was ≥65 beats/min, additional oral beta-blockers (metoprolol, 50 mg, single dose, 1 h before scan) were provided if tolerated. First, a prospectively triggered coronary calcium scan was performed before MSCT angiography with identical parameters for 16- and 64-slice MSCT systems: collimation 4 x 3.0 mm, gantry rotation time 500 ms, tube voltage and tube current 120 kV and 200 mA, respectively. The temporal window was set at 75% after the R-wave for electrocardiographically triggered prospective reconstruction.

Sixteen-slice MSCT coronary angiography was performed according to the protocol described elsewhere.[10] The following parameters were applied for 64-slice MSCT coronary angiography: collimation of 64 x 0.5 mm; tube rotation time of 400, 450, or 500 ms, depending on the heart rate; tube current 300 mA at 120 kV. Nonionic contrast material was administered in the antecubital vein with an amount of 80 to 105 ml, depending on the total scan time, and a flow rate of 5 ml/s (Iomeron 400, Bracco Altana Pharma, Konstanz, Germany). Automated detection of peak enhancement in the aortic root was used for timing of the scan. All images were acquired during an inspiratory breath hold of approximately 10 s, with simultaneous registration of the patient's electrocardiogram. With the aid of a segmental reconstruction algorithm, data of 1, 2, or 3 consecutive heartbeats were used to generate a single image.

To evaluate the presence of coronary artery plaques, reconstructions in diastole (typically 75% of the cardiac cycle) were generated with a slice thickness of 0.5 mm at an increment of 0.3 mm. If motion artefacts were present, additional reconstructions were made in different time points of the R-R interval. Axial data sets were transferred to a remote workstation (Vitrea 2, Vital Images, Plymouth, Minnesota) for postprocessing and subsequent evaluation.

MSCT data analysis

Coronary artery calcium score

The coronary artery calcium score was assessed with the application of dedicated software (Vitrea 2). Coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU. An overall Agatston score was recorded for each patient.

Coronary plaque assessment

For the current study, all MSCT angiograms were evaluated within a time frame of 2 weeks by 2 experienced observers unaware of the clinical history of the patients, using a standard analysis (see later text). In case of disagreement, a joint reading was performed and a consensus decision was reached. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification.[11] Only segments with a diameter >1.5 mm (as measured on the MSCT coronary angiogram) were included. First, each segment was classified as interpretable or not. Predefined, patients were excluded from the analysis in case of: 1) an uninterpretable proximal or mid segment, or 2) more than 3 uninterpretable segments in general.

Then, the interpretable segments were evaluated for the presence of any atherosclerotic plaque using axial images and curved multiplanar reconstructions. Coronary plaques were defined as structures >1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue, as previously described.[12] One coronary plaque was assigned per coronary segment. Subsequently, the type of plaque was determined using the following classification: 1) noncalcified plaques, plaques having lower density compared with the contrast-enhanced vessel lumen; 2) calcified plaques, plaques with high density; and 3) mixed plaques, plaques with noncalcified and calcified elements within a single plaque. Finally, it was determined whether the lesion was obstructive or not, using a threshold of 50% luminal narrowing. For each patient, the number of diseased coronary segments, number of segments with obstructive lesions, and number of each type of plaque was calculated. Patients without coronary artery calcium or coronary plaques on MSCT were considered normal; an abnormal MSCT was defined in the presence of ≥1 coronary plaque. Abnormal patients were further classified as having obstructive coronary plaques (≥50% luminal narrowing) in 1 or more coronary arteries, as well as having obstructive coronary lesions in the left main (LM) and/or left anterior descending (LAD) coronary arteries.

Follow-up

Follow-up information was obtained by either clinical visits or telephone interviews. Hospital records of all patients were screened for the occurrence of clinical events to confirm the obtained information. Clinical end points were the occurrence of: 1) cardiac death, 2) nonfatal infarction, 3) unstable angina requiring hospitalization, or 4) revascularization. Cardiac death was defined as death caused by acute myocardial infarction, ventricular arrhythmias, or refractory heart failure. Nonfatal myocardial infarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram.[13]

Statistical analysis

Categorical baseline characteristics are expressed as numbers and percentages, and compared between 2 groups with the chi-square test. Continuous variables are expressed as mean (standard deviation) and compared with the 2-tailed *t* test for independent samples. When not normally distributed, continuous variables are expressed as medians (25th to 75th percentile range) and compared using a nonparametric Mann-Whitney test.

To identify the association between MSCT variables and outcomes, Cox regression analysis was used. A composite end point of cardiac death, nonfatal infarction, unstable angina requiring hospitalization, and revascularization was used. First, univariate analysis of baseline clinical characteristics and MSCT variables was performed to identify potential predictors. Hazard ratios were calculated with 95% confidence intervals as an estimate of the risk associated with a particular variable. To determine independent predictors of the composite end point, multivariate analysis of MSCT variables with $p \leq 0.05$ in the univariate analysis was performed, which was corrected for the baseline characteristics with $p \leq 0.5$ in the univariate analysis.

Cumulative event rates as a function over time were obtained by the Kaplan-Meier method. Event curves of the composite end point (cardiac death, nonfatal infarction, unstable angina requiring hospitalization, revascularization) and hard cardiac events (cardiac death, nonfatal infarction, and unstable angina requiring hospitalization) were compared using the log-rank test.

Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc., Chicago, Illinois) and SAS software (version 6.12, SAS Institute Inc., Cary, North Carolina), and p values <0.05 were considered statistically significant.

Results

Patient characteristics

In total, 104 consecutive patients were enrolled in the present study. In 4 patients, an elevated and/or irregular heart rate during MSCT data acquisition rendered the MSCT data set uninterpretable, and these patients were excluded from the analysis. As a result, 100 patients (73 men, mean age 59±12 years) were included in the study (15 patients were included in a previous study on the diagnostic accuracy of MSCT in direct comparison with invasive angiography).[10] Baseline characteristics are provided in Table 1.

Table 1. Characteristics of the study population and comparison between patients with and without events

	All patients (n=100) n (%)	Patients with events (n=26) n (%)	Patients without events (n=74) n (%)
Clinical characteristics			
Age (yrs)* (mean ± SD)	59±12	63±10	58±12
Male gender	73 (73%)	20 (77%)	53 (72%)
Obesity	20 (20%)	4 (18%)	16 (22%)
Diabetes	21 (21%)	5 (19%)	16 (22%)
Hypercholesterolemia	50 (50%)	15 (58%)	35 (47%)
Hypertension	44 (44%)	9 (35%)	35 (47%)
Family history of CAD	42 (42%)	12 (46%)	30 (41%)
Smoking	39 (39%)	13 (50%)	26 (35%)
EuroSCORE value* (mean ± SD)	2.4±2.2	3.4±2.5	2.1±2
Cardiac history			
Suspected CAD	65 (65%)	14 (54%)	51 (65%)
Previous MI	33 (33%)	11 (42%)	22 (30%)
Previous revascularization	31 (31%)	10 (39%)	21 (28%)?
Medical therapy			
ACE inhibitors	37 (37%)	7 (27%)	30 (41%)
Nitrates	14 (14%)	4 (15%)	10 (14%)
Beta-blockers	56 (56%)	16 (62%)	40 (54%)
Aspirin	54 (54%)	17 (65%)	37 (50%)
Statins	50 (50%)	12 (46%)	38 (51%)

* $p<0.05$ between patients with and without events.

ACE, angiotensin converting enzyme; CAD, coronary artery disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MI, myocardial infarction.

Briefly, 65 patients (65%) presented with suspected CAD at the time of MSCT, whereas CAD was known in the remaining 35 patients (35%) (33 patients had previous myocardial infarction, 31 patients had previous percutaneous coronary intervention). In total, 55 patients underwent 16-slice MSCT and 45 underwent 64-slice MSCT.

MSCT

The MSCT characteristics are provided in Table 2. Only coronary segments with sufficient lumen diameter for evaluation of the presence of plaques were included in the analysis. After exclusion of 33 (2%) coronary segments with stents and 19 (1%) nonevaluable segments because of motion artifacts, plaque burden was evaluated in 1,298 segments. CAD was completely absent in 20 patients. In the remaining 80 patients, 345 coronary segments with plaques were observed, of which 47 (14%) contained noncalcified plaques, 109 (31%) mixed plaques, and 189 (55%) calcified plaques.

Table 2. MSCT Characteristics of the study population and comparison between patients with and without events

	All patients (n=100)	Patients with events (n=26)	Patients without events (n=74)
Total Agatston score* (median, 25th-75th percentile)	147 (0-383)	311 (122-552)	62 (0-309)
Coronary plaques on MSCT* (number (%))	80 (80%)	26 (100%)	54 (73%)
Obstructive CAD* (number (%))	32 (32%)	20 (77%)	12 (16%)
Obstructive CAD in LM/LAD* (number (%))	23 (23%)	18 (69%)	5 (7%)
Nr of segments with plaques* (median, 25th-75th percentile)	3 (1-5)	5 (4-7)	2 (0-5)
Nr of segments with obstructive plaques* (median, 25th-75th percentile)	0 (0-1)	1.5 (0.8-3)	0
Nr of segments with non-calcified plaques (median, 25th-75th percentile)	0 (0-1)	0 (0-1)	0 (0-1)
Nr of segments with mixed plaques* (median, 25th-75th percentile)	0 (0-2)	2 (0.8-3.3)	0 (0-2)
Nr of segments with calcified plaques* (median, 25th-75th percentile)	1 (0-3)	2.5 (1-4)	1 (0-3)

* $p<0.05$ between patients with and without events.

CAD, coronary artery disease; LAD, left anterior descending coronary artery; LM, left main coronary artery; MSCT, multi-slice computed tomography.

In 71 (21%) segments of 32 (32%) patients, plaques were regarded as obstructive (≥50% luminal narrowing). Thirty-two (9%) segments with obstructive lesions in 23 (23%) patients were located in the LM and/or LAD coronary artery. In Figure 1, examples of different MSCT observations, including normal coronary arteries, nonobstructive CAD, and obstructive CAD in the LM, are shown.

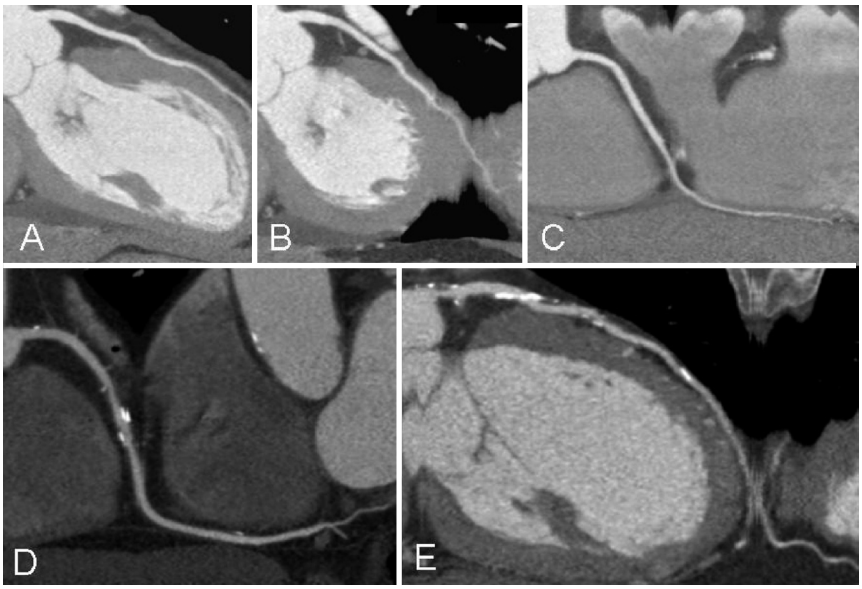

Figure 1. Examples of different multi-slice computed tomography observations (A, B, C). Curved multiplanar reconstructions of, respectively, the left anterior descending coronary artery (LAD), left circumflex coronary artery, and right coronary artery (RCA) of a patient with normal coronary arteries are provided. (D) Curved multiplanar reconstruction of the RCA is provided, showing diffuse coronary artery disease without obstructive lesions. (E) Stenosis of the left main coronary artery as well as proximal LAD can be observed.

Follow-up results

During a mean follow-up of 16 months (median 13 months, interquartile range 5 to 39 months), 33 events occurred in 26 patients (with 7 events occurring repeatedly). One patient (1%) died of acute myocardial infarction. Nonfatal myocardial infarction occurred in 3 patients (3%), and unstable angina requiring hospitalization occurred in 4 patients (4%, with 1 also undergoing revascularization). A total of 24 patients (24%) underwent coronary revascularization; percutaneous coronary intervention was performed in 17 patients, whereas the remaining 7 patients underwent coronary artery bypass grafting. The decision for revascularization was based on worsening angina and/or the presence of ischemia on noninvasive testing.

Table 3. Univariate predictors of events

Clinical characteristics	HR (95% CI)	p-value
Age (yrs)	1.0 (0.99 -1.0)	0.12
Male gender	0.86 (0.34-2.2)	0.75
Obesity	0.71 (0.24-2.0)	0.52
Diabetes	0.85 (0.32-2.3)	0.74
Hypercholesterolemia	1.4 (0.62-3.0)	0.45
Hypertension	0.62 (0.28-1.3)	0.24
Family history of CAD	1.3 (0.61-2.9)	0.47
Smoking	1.7 (0.77-3.6)	0.19
Previous revascularization	1.4 (0.62-3.1)	0.63
Previous infarction	1.5 (0.67-3.2)	0.92
EuroSCORE value	1.1 (0.99-1.3)	0.08
Medical therapy		
ACE inhibitors	0.65 (0.28-1.6)	0.34
Nitrates	1.0 (0.36-3.0)	0.94
Beta-blockers	1.4 (0.61-3.0)	0.46
Aspirin	1.8 (0.80-4.0)	0.15
Statins	0.86 (0.40-1.9)	0.70
MSCT characteristics		
Total Agatston score	1.1 (1.0-1.1)	0.06
Presence of coronary plaques on MSCT	8.0 (1.1-59)	0.04
Abnormal coronary arteries, non-obstructive CAD (as compared to no CAD)	2.7 (0.32-22)	0.36
Abnormal coronary arteries, obstructive CAD (as compared to no CAD)	22 (2.9-166)	0.003
Abnormal coronary arteries, non-obstructive CAD in LM/LAD	3.1 (0.39-25)	0.29
Abnormal coronary arteries, obstructive CAD in LM/LAD	36 (4.7-276)	0.0006
Nr of segments with plaques*	1.3 (1.1-1.4)	0.0005
Nr of segments with obstructive plaques*	1.8 (1.5-2.1)	<0.0001
Nr of segments with non-calcified plaques*	1.1 (0.78-1.6)	0.43
Nr of segments with mixed plaques*	1.5 (1.3-1.9)	0.0002
Nr of segments with calcified plaques*	1.1 (0.98-1.3)	0.1

* Ratio per segment.

ACE, angiotensin converting enzyme; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LAD, left anterior descending coronary artery; LM, left main coronary artery; MI, myocardial infarction; MSCT, multi-slice computed tomography.

Predictors of events

Baseline and clinical characteristics of patients with and without events are described in Table 1. Patients presenting with events during follow-up were significantly older (p=0.03) and had worse clinical condition, as indicated by an elevated European System for Cardiac Operative Risk Evaluation value (p=0.01). No significant differences in risk factors for CAD and use of medication were observed.

Differences in MSCT characteristics of patients with and without events are summarized in Table 2. Patients with events had more extensive atherosclerosis on MSCT, as reflected by a higher coronary calcium score and a higher number of segments showing (obstructive) plaques. Also, relatively more mixed and calcified plaques were observed as compared with patients without events.

In Table 3, the univariate analysis of both clinical and MSCT characteristics to predict events is summarized. In the multivariate analysis (Table 4), MSCT characteristics that were significant during univariate analysis were corrected for baseline characteristics with p≤0.5 during univariate analysis, whereas the type of scanner (16- versus 64-slice MSCT) used was also included in the analysis. As indicated in Table 4, the remaining significant independent predictors of cardiac events in the multivariate analysis were the presence of coronary plaques, obstructive CAD, LM/LAD disease, number of coronary segments with plaques, number of coronary segments with obstructive plaques, and number of coronary segments with mixed plaques.

Table 4. Multivariate predictors of events, corrected for baseline variables

MSCT characteristics	Multivariate	p-value
Presence of coronary plaques on MSCT	8.8 (1.1-70)	0.04
Obstructive CAD	28 (3.3-239)	0.002
Obstructive CAD in LM/LAD	35 (4.3-288)	0.0009
Nr of segments with plaques*	1.3 (1.1-1.6)	0.0009
Nr of segments with obstructive plaques*	1.8 (1.5-2.2)	<0.0001
Nr of segments with mixed plaques*	1.6 (1.2-2.0)	0.0003

* Ratio per segment.

Data are Cox's proportional hazard ratios (95% confidence intervals).

MSCT, multi-slice computed tomography.

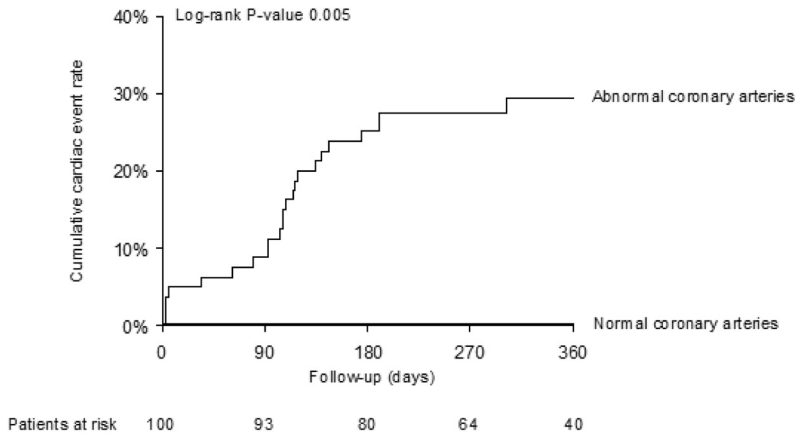

Figure 2. Kaplan-Meier curves for all events in patients with normal and abnormal coronary arteries on MSCT. All events indicate cardiac death, nonfatal infarction, unstable angina requiring hospitalization, and revascularization. MSCT, multi-slice computed tomography.

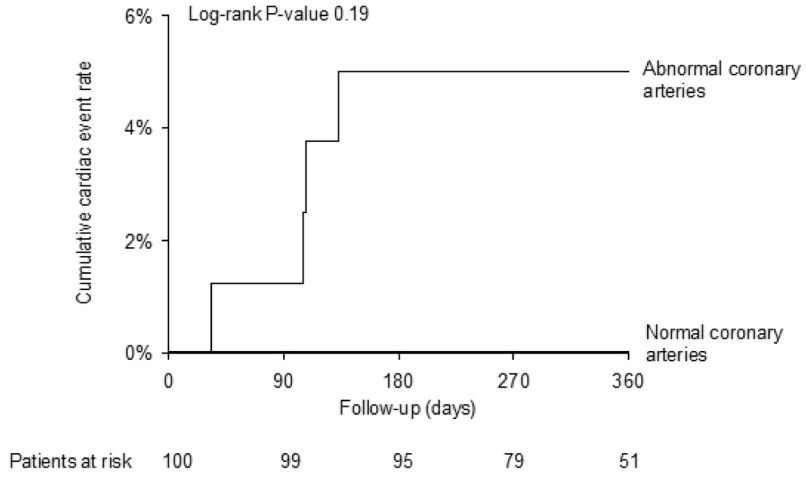

Figure 3. Kaplan-Meier curves for hard cardiac events in patients with normal and abnormal coronary arteries on MSCT. Hard cardiac events indicate cardiac death, nonfatal infarction, and unstable angina requiring hospitalization. MSCT, multi-slice computed tomography.

Survival analysis

Kaplan-Meier survival curves are provided in Figures 2 to 5. As can be derived from Figure 2, no events occurred in patients with normal coronary arteries on MSCT, whereas a first-year event rate (including all events) of 30% was observed in patients with any CAD on MSCT (log-rank p value =0.005). Excluding revascularizations resulted in a first-year hard cardiac event rate of 5% in patients with CAD on MSCT, as compared with 0% in patients with completely absent CAD on MSCT (log-rank p value =0.19) (Figure 3).

In Figure 4, the relationship between the severity of CAD and the occurrence of events was further explored, showing an increased event rate in patients with obstructive CAD (63%) compared with patients without CAD (0%) or nonobstructive CAD (8%) (log-rank p value <0.001). Finally, LM/LAD disease was found to be associated with the highest event rate (77%), as shown in Figure 5 (log-rank p value <0.001).

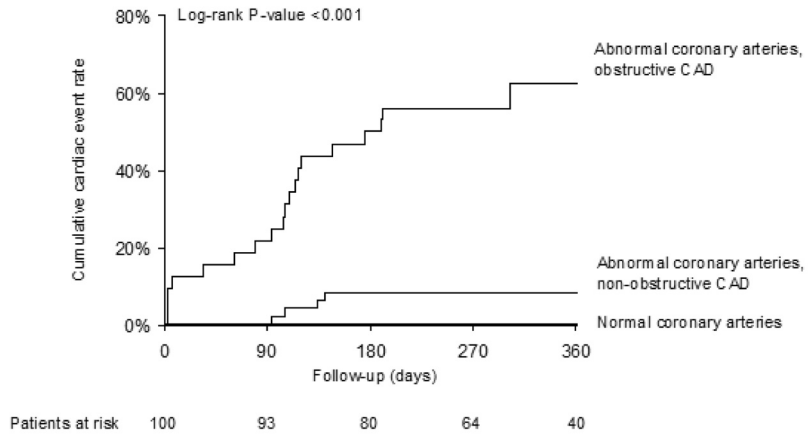

Figure 4. Kaplan-Meier curves for all events in patients with normal coronary arteries, nonobstructive CAD, and obstructive CAD on MSCT.

All events indicate cardiac death, nonfatal infarction, unstable angina requiring hospitalization, and revascularization. CAD, coronary artery disease; MSCT, multi-slice computed tomography.

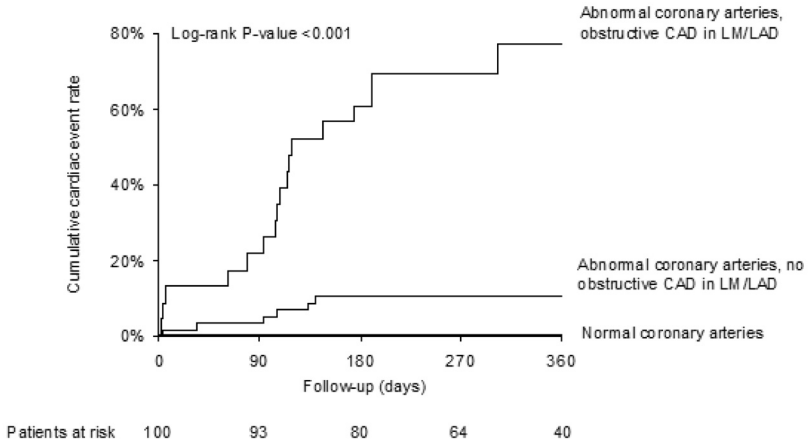

Figure 5. Kaplan-Meier curves for all events in patients with normal coronary arteries, patients without obstructive CAD in LM/LAD, and patients with obstructive CAD in LM and/or LAD on MSCT.
All events indicate cardiac death, nonfatal infarction, unstable angina requiring hospitalization, and revascularization. LAD, left anterior descending coronary artery; LM, left main coronary artery; CAD, coronary artery disease; MSCT, multi-slice computed tomography.

Discussion

In the present study, MSCT coronary angiography provided independent prognostic information for predicting cardiac events. Patients with completely absent CAD on MSCT coronary angiography had an excellent prognosis (0% event rate), whereas an increased event rate (30%) was observed in patients with CAD on MSCT. Furthermore, the risk of cardiac events increased with the extent of CAD as observed on MSCT, and patients with obstructive lesions (particularly in the LM and LAD) were shown to be at the greatest risk for cardiac events. Even after correction for baseline clinical variables such as age and risk factors, MSCT variables reflecting coronary plaque burden, including the severity, extent, and location of atherosclerosis, remained independent predictors of cardiac events.

The prognostication and subsequent management of patients with known or suspected CAD in current practice relies on initial clinical evaluation, with the low-risk patients being reassured and the high-risk patients being referred for invasive angiography.[14] However, the majority of these patients are in the intermediate risk group, in whom prognosis and subsequent management is less well defined. Accordingly, these patients need additional testing with 1 or more of the established noninvasive modalities, which include exercise electrocardiography, stress SPECT imaging, or stress echocardiography.[14] All these techniques aim at detecting ischemia. Exercise electrocardiography is not an ideal

modality because of the suboptimal accuracy, and imaging of stress-induced perfusion abnormalities or systolic wall motion abnormalities may be preferred; indeed, average sensitivity and specificity of 87% and 73% to detect CAD have been reported for SPECT versus 82% and 84% for stress echocardiography.[15,16] In addition, these tests proved to be predictive of future cardiac events when abnormalities were found and were associated with a low risk for events when the test results were normal.[17-19]

Multi-slice computed tomography coronary angiography is a highly accurate, noninvasive imaging technique for the diagnosis of CAD; in particular, the negative predictive value of MSCT approaches 100%, allowing CAD to be ruled out.[20,21]

The current study explored the prognostic value of MSCT in a symptomatic patient population with known or suspected CAD and a high prevalence of conventional risk factors. Consequently, the pretest likelihood of CAD was high in this population, and even in patients without known disease, CAD was present on MSCT in 69%. Not surprisingly, therefore, high cardiac event rates were observed. Most importantly, however, a 100% event-free survival was noted in patients without any abnormalities on MSCT, highlighting an excellent negative predictive value of a normal MSCT. This finding is of major clinical relevance, because these patients may indeed be safely reassured without need for further testing. Patients with coronary atherosclerosis identified on MSCT were shown to have a worse prognosis. More detailed analysis showed that although the risk of events was considerably higher in patients with obstructive CAD, patients with nonobstructive CAD still were at elevated risk as compared with patients without CAD. Indeed, previous studies support the notion that plaque composition (in addition to stenosis severity) is predictive of events. Moreover, Mann et al [22] showed in a postmortem study that lipid core size and minimal cap thickness, 2 major determinants of plaque vulnerability, were not related to absolute plaque size or degree of stenosis. Accordingly, vulnerable plaques may occur across the full spectrum of severity of stenosis, underlining that also nonobstructive lesions may contribute to coronary events.[23,24] Because less obstructive plaques are more frequent than severely obstructive plaques, coronary occlusion and myocardial infarction may in fact most frequently arise from mild to moderate stenoses.[23,25–28] Pooling of these angiographic studies showed that 68% of myocardial infarctions were attributable to so-called “angiographically silent” lesions (luminal narrowing <50%), whereas only 14% could be assigned to a severe stenotic lesion (>70%).[29] In line with these observations, multivariate analysis of the possible predictors of cardiac events in the present study showed that nonobstructive CAD was indeed an independent predictor of future cardiac events. Of interest, the presence of mixed plaques, which may represent less advanced

and possibly less stabilized atherosclerosis as compared with dense calcified lesions,[30] was shown to be an independent predictor as well. However, further investigations are clearly needed to support these observations.

Nonetheless, considering individual lesions, the likelihood of progression to coronary occlusion (and subsequent myocardial infarction) remains highest for severe obstructive lesions.[23,25,26] Indeed, prospective evaluation of nonbypassed coronary segments, as was performed in the CASS (Coronary Artery Surgery Study), showed that during a 5-year follow-up only 0.7% and 2.3% of segments with narrowing of respectively <5% and 5% to 49% resulted in coronary occlusion.[25] In contrast, occlusion occurred in 10.1% and even 23.6% of lesions with narrowing 50% to 80% and 81% to 95%, respectively. In agreement, high event rates were observed for patients with obstructive CAD in the present study. More detailed analysis showed that hazard ratios were highest for patients with obstructive CAD in either the LM or LAD coronary arteries. Indeed previous studies showed that patients with severe proximal LAD disease are at high risk;[31–33] for example, Califf et al [34] reported a 59% event-free survival at 5 years in patients with 3-vessel disease and proximal LAD disease. Accordingly, early identification of these patients with MSCT will be crucial to optimize therapy.

Study limitations

The prognostic value of MSCT in the present study was evaluated in patients presenting with a wide spectrum of different conditions, including patients with no previous history of CAD and patients with previous myocardial infarction and revascularization. Accordingly, treatment strategies may have differed substantially within the studied population, and future studies will need to address the prognostic role of MSCT coronary angiography in more homogeneous patient populations. Also, the study population was small, and some clinically relevant predictors may not have reached statistical significance. Studies in larger cohorts (with longer follow-up) are clearly warranted to confirm these initial results.

Conclusions

This is the first study to show the independent prognostic value of MSCT coronary angiography over baseline clinical risk factors in patients presenting with chest pain. An excellent prognosis (0% event rate) was noted in patients with a normal MSCT. The presence of CAD (either nonobstructive or obstructive atherosclerotic lesions) was associated with an event rate of 30%. The event rate was highest in the presence of obstructive lesions and when lesions were located in the LM/LAD coronary arteries. Future studies are needed to further define the prognostic value of MSCT.

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Chapter 8

Head-to-Head Comparison of Coronary Plaque Evaluation Between Multi-Slice Computed Tomography and Intravascular Ultrasound Radiofrequency Data Analysis

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Abstract

Aims: The purpose of this study was to perform a head-to-head comparison of plaque observations with multi-slice computed tomography (MSCT) to virtual histology intravascular ultrasound (VH IVUS).

Background: The VH IVUS allows in vivo coronary plaque characterization with high spatial resolution. Noninvasively, plaques may be evaluated with MSCT, but limited data are available.

Methods: A total of 50 patients underwent 64-slice MSCT followed by VH IVUS. The Agatston score was evaluated on MSCT in coronary segments where IVUS was performed. Plaques were classified on MSCT as noncalcified, mixed, and calcified. Four plaque components (fibrotic, fibro-fatty, and necrotic core tissues, and dense calcium) were identified on VH IVUS, and the presence of thin-cap fibroatheroma was evaluated.

Results: A moderate correlation was observed between the Agatston score and calcium volume on VH IVUS ($r=0.69$, $p<0.0001$). In total, 168 coronary plaques were evaluated (48 (29%) noncalcified, 71 (42%) mixed, 49 (29%) calcified). As compared with calcified plaques, noncalcified plaques contained more fibrotic (60.90±9.21% versus 54.60±8.33%, $p=0.001$) and fibro-fatty tissues (28.11±13.03% versus 21.37±9.75%, $p=0.006$) on VH IVUS. Mixed and calcified plaques contained more dense calcium (7.61±8.94% versus 2.68±3.01%, $p=0.001$; 10.18±6.71% versus 2.68±3.01%, $p<0.0001$, respectively). Thin-cap fibroatheromas were most frequently observed in mixed plaques as compared with noncalcified and calcified plaques (32%, 13%, 8%, $p=0.002$, respectively).

Conclusions: A good correlation was observed between calcium quantification on MSCT and VH IVUS. In addition, plaque classification on MSCT paralleled relative plaque composition on VH IVUS, although VH IVUS provided more precise plaque characterization. Mixed plaques on MSCT were associated with high-risk features on VH IVUS.

Introduction

During the last decade, multi-slice computed tomography (MSCT) coronary angiography has rapidly matured into a technique that could be used as an alternative imaging modality to detect coronary stenoses in patients with suspected coronary artery disease (CAD). Moreover, the technique allows direct visualization of coronary plaques, in contrast to conventional coronary angiography. Accordingly, MSCT may also have the potential to provide information on plaque composition in addition to the degree of stenosis.[1-4] Indeed, Schroeder et al[4] showed that in comparison with grayscale intravascular ultrasound (IVUS), differentiation between noncalcified, intermediate, and calcified plaques is possible on MSCT based on the differences in the average plaque signal intensity. Moreover, MSCT observations may be different among various clinical presentations. For example, a lower prevalence of completely calcified plaques on MSCT was demonstrated in previous studies in patients presenting with acute coronary syndromes.[5–7]

Potentially, more detailed information on plaque composition could be derived from virtual histology IVUS (VH IVUS). This technique has recently been introduced as a novel IVUS modality. This invasive imaging technique allows accurate in vivo evaluation of 4 coronary plaque components, namely fibrotic, fibro-fatty, and necrotic core tissues and dense calcium.[8] Indeed, as compared with histopathology, VH IVUS allowed detection of the necrotic core with a predictive accuracy of 88.3%, whereas the accuracy to detect regions of dense calcium, was as high as 96.5%.[8] In addition, differences in plaque composition have been demonstrated in different clinical settings using this technique. In patients presenting with acute coronary syndromes, the amount of necrotic core tissue and the density of thin-cap fibroatheromas (TCFA) (features that are associated with high risk of plaque rupture) were shown to be significantly higher as compared with patients with stable CAD.[8–10]

As a consequence, VH IVUS could provide more insight into plaque composition on MSCT. In addition, it is unclear which coronary plaques on MSCT may represent lesions with high-risk features. However, no systematic comparisons between MSCT and VH IVUS are currently available. Accordingly, the purpose of the study was to perform a head-to-head comparison of coronary plaque composition as determined by MSCT to VH IVUS. With regard to plaque classification, we expected to demonstrate a fair relation between plaque type (noncalcified, mixed, or calcified) as determined by MSCT versus relative composition as determined by VH IVUS. However due to the higher spatial resolution of VH IVUS, we expected to observe more details on VH IVUS. Finally, noncalcified and mixed lesions on MSCT appear to occur more frequently in unstable conditions, and therefore, we expected noncalcified and mixed plaques to be related to high-risk features on VH IVUS.

Methods

Patient population and study protocol

In total, 50 patients scheduled for conventional coronary angiography based on clinical presentation were prospectively included in the study. All patients underwent 64-slice MSCT coronary angiography, followed by invasive coronary angiography in combination with VH IVUS. Noninvasive and invasive examinations of coronary plaques were performed within 1 month. The clinical history of the patients was evaluated prior to conventional coronary angiography to ensure that no acute coronary events or worsening of angina occurred between examinations.

Only patients without contraindications to MSCT and IVUS were included in the study. Exclusion criteria for MSCT were (supra)ventricular arrhythmias, renal insufficiency (serum creatinine >120 μmol/l), and known allergy to iodine contrast media. Exclusion criteria for IVUS were severe vessel tortuousness or occlusion.

The study protocol was approved by the local ethics committee and informed consent was obtained from all patients.

MSCT

Data acquisition

The 64-slice MSCT coronary angiography was performed using a Toshiba Aquilion (Toshiba Medical Systems, Tokyo, Japan) scanner. First, a coronary calcium scan without contrast was obtained, followed by 64-slice MSCT coronary angiography performed during electrocardiographic gating and the administration of nonionic contrast at 5 ml/s according to the protocol as described previously.[11] If the heart rate was ≥65 beats/min, additional oral beta-blockers (metoprolol, 50 or 100 mg, single dose, 1 h prior to the examination) were provided if tolerated. After acquisition, the data were reconstructed and transferred to a remote workstation for post-processing. When extensive coronary calcifications were present, sharp reconstruction algorithms were used to reduce partial volume effects of coronary calcium.

Data analysis

Data were evaluated using a remote workstation with dedicated software (Vitrea 2, Vital Images, Minnetonka, Minnesota, or Advantage, GE Healthcare, Milwaukee, Wisconsin). The MSCT angiograms and calcium scans were evaluated by 2 experienced observers who were unaware of the clinical characteristics and the IVUS findings. Disagreements were immediately resolved in consensus. First, coronary artery calcium score was assessed in each coronary segment. For this purpose, side branches and coronary ostia were used as landmarks, and

the contrast-enhanced images were viewed for verification of the segmentation. In addition, the intra- and interobserver agreement of calcium scoring on a segmental basis was evaluated. For the intraobserver agreement analysis, the same observer remeasured segmental coronary calcium scores after 2 months. The difference between the measured calcium scores was calculated for each segment. The mean difference for all measurements was calculated to express the intraobserver agreement. For the interobserver agreement analysis, a second observer remeasured the segmental coronary calcium scores. For each segment, the difference between these measurements by the 2 observers was calculated. The mean difference was used to express interobserver agreement.

Subsequently, the presence of coronary plaques was visually evaluated on the contrast-enhanced coronary angiograms using axial images and curved multiplanar reconstructions. Coronary plaques were defined as structures >1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding tissue, as previously described.[2] Side branches and coronary ostia were used as landmarks to define the location of plaques in the arteries. After localization of a coronary plaque, the start and the end positions were visually identified and verified according to the criteria mentioned above. In cases when atherosclerosis was diffusely present over the entire course of the artery, plaques were evaluated per coronary segment. Accordingly, landmarks defining the coronary segments were used to indicate the start and the end positions in these cases. Plaques were visually classified as follows: 1) noncalcified = plaque having lower density compared with the contrast enhanced vessel lumen present without any calcification discernible; 2) calcified plaque = plaque with predominantly high density present; and 3) mixed plaque = plaque with noncalcified and calcified elements present.

Conventional coronary angiography

Conventional invasive coronary angiography was performed according to standard protocols. Coronary angiograms were evaluated by an experienced observer blinded to all study results; the presence of an obstructive lesion was defined as ≥50% luminal narrowing in 2 orthogonal views.

VH IVUS

Data acquisition

For each IVUS examination, a 20-MHz, 2.9-F, phased-array IVUS catheter (Eagle Eye, Volcano Corp., Rancho Cordova, California) was used. After administration of intracoronary nitrates, the IVUS catheter was introduced to the distal coronary artery. Using an automated pullback device, the transducer was withdrawn at a continuous speed of 0.5 mm/s up to

the coronary ostium. Cine runs before and during contrast injection were performed to define the starting position of the IVUS catheter. The electrocardiographically triggered IVUS radiofrequency signals were acquired and stored for off-line analysis.

Data analysis

Off-line VH IVUS analyses were performed using dedicated software (pcVH 2.1, Volcano Corp.) by an experienced observer blinded to baseline patient characteristics. After automated detection, external elastic membrane and lumen borders were manually edited. The contours of the external elastic membrane and the lumen-intima interface enclosed an area defined as coronary plaque plus media area. Atherosclerotic coronary plaques were characterized based on spectral analysis of IVUS backscattered signals, as described and validated previously.[8,12] Four tissues were differentiated, including fibrotic tissue being labeled in dark green, fibro-fatty in light green, necrotic core in red, and dense calcium in white (Figure 1).

The region of interest corresponding to plaques observed on MSCT was defined using side branches and coronary ostia as landmarks. For each region of interest, the mean value of the 4 relative compositional quantitative plaque parameters was obtained. In addition, the volume of dense calcium in coronary segments where IVUS examination was performed was measured in all patients. Finally, the presence of IVUS-derived TCFA was evaluated in 3 consecutive frames within 10 mm of the minimum lumen area slice of each plaque. The TCFAs were defined as lesions fulfilling the following criteria: 1) plaque burden >40%; 2) the presence of confluent necrotic core of >10%; and 3) no evidence of an overlying fibrous cap (Figure 2B).[10,13]

Comparison of MSCT and VH IVUS

To ensure that identical plaques were assessed by MSCT and VH IVUS, coronary ostia and side branches were used as landmarks and distances from the landmarks to the target lesions were measured. The distances were measured on multiplanar reconstructions of the coronary arteries on MSCT. On IVUS, the corresponding plaque was identified using longitudinally reconstructed IVUS datasets.[3] The transversal IVUS sections were further inspected and the start and the finish frames of the lesions were depicted on electrocardiographically triggered IVUS datasets of VH IVUS analyses.

Statistical analysis

Categorical variables are expressed as numbers (percentages) and compared between groups with 2-sided chi-square test or Fisher exact test. Continuous variables are expressed as mean (standard deviation) and compared with 1-way analysis of variance test. In case of significant differences, the differences between the samples were further evaluated using post hoc Bonferroni test. Correlation between the Agatston calcium score and the volume of dense calcium on VH IVUS were assessed with Pearson correlation analysis.

The p values <0.05 are considered as statistically significant. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc., Chicago, Illinois).

Results

Patient characteristics

The MSCT coronary angiography and VH IVUS imaging were performed in 50 patients. All MSCT scans and IVUS images were of diagnostic quality, and no patient was excluded from analysis. The baseline patient characteristics are provided in Table 1. Briefly, 31 patients (62%) were males, and the average age was 60±11 years.

Table 1. Baseline characteristics of the study population

	n=50
Male gender	31 (62%)
Age (yrs)	60±11
Obesity	9 (18%)
Type 2 diabetes mellitus	10 (20%)
Hypercholesterolemia	30 (60%)
Hypertension	28 (56%)
Family history of CAD	25 (50%)
Smoking	21 (42%)
Typical angina	26 (52%)
Previous myocardial infarction	4 (8%)
Previous PCI	8 (16%)

CAD, coronary artery disease; PCI, percutaneous coronary intervention.

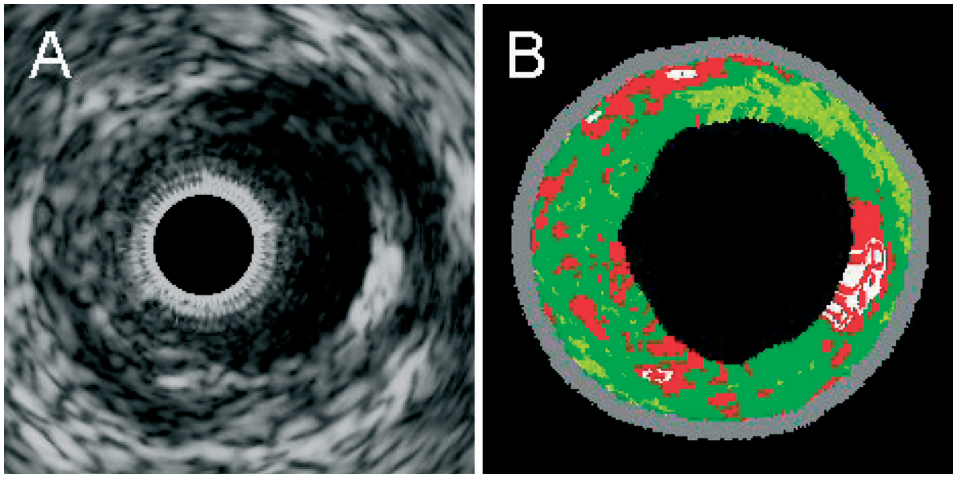

Figure 1. Plaque characterization by VH IVUS.
A traditional grayscale intravascular ultrasound (IVUS) cross-sectional image of coronary plaque (A). (B) Corresponding image using virtual histology IVUS (VH IVUS), depicting different color-coded tissues based on spectral analysis of the radiofrequency ultrasound signals. The components are indicated by dark green for fibrotic tissue; light green for fibro-fatty tissue; red for necrotic core; white for dense calcium.

Agatston calcium score on MSCT versus calcium content on VH IVUS

The correlation between the Agatston calcium score on MSCT and the volume of dense calcium on VH IVUS in segments in which IVUS examination was performed is presented in Figure 3. A significant correlation was observed between the Agatston calcium score and the volume of dense calcium on VH IVUS ($r=0.69$, $p<0.0001$). In addition, intraobserver and interobserver agreement was evaluated. A good intraobserver agreement was observed for the quantification of calcium score per coronary segment on MSCT (mean difference in segmental calcium score 3.2±5.4). Similarly, a good interobserver agreement was observed and the mean difference in segmental calcium scores was 3.4±6.5 between both observers.

Plaque type on MSCT versus composition on VH IVUS

An example of the different plaque types as identified on MSCT and their corresponding VH IVUS images are provided in Figure 2. In total, 168 coronary plaques fulfilled the predefined criteria and were included in the analysis. Of these lesions, 40 (24%) plaques were obstructive, whereas the remaining 128 (76%) lesions were nonobstructive (as determined on conventional invasive coronary angiography). Based on the MSCT scans, 48 (29%) plaques were classified as noncalcified, 71 (42%) as mixed, and 49 (29%) as

calcified. Thirteen (27%) noncalcified plaques, 17 (24%) mixed plaques, and 10 (20%) calcified plaques were classified as obstructive stenoses on conventional invasive coronary angiography (p=0.7).

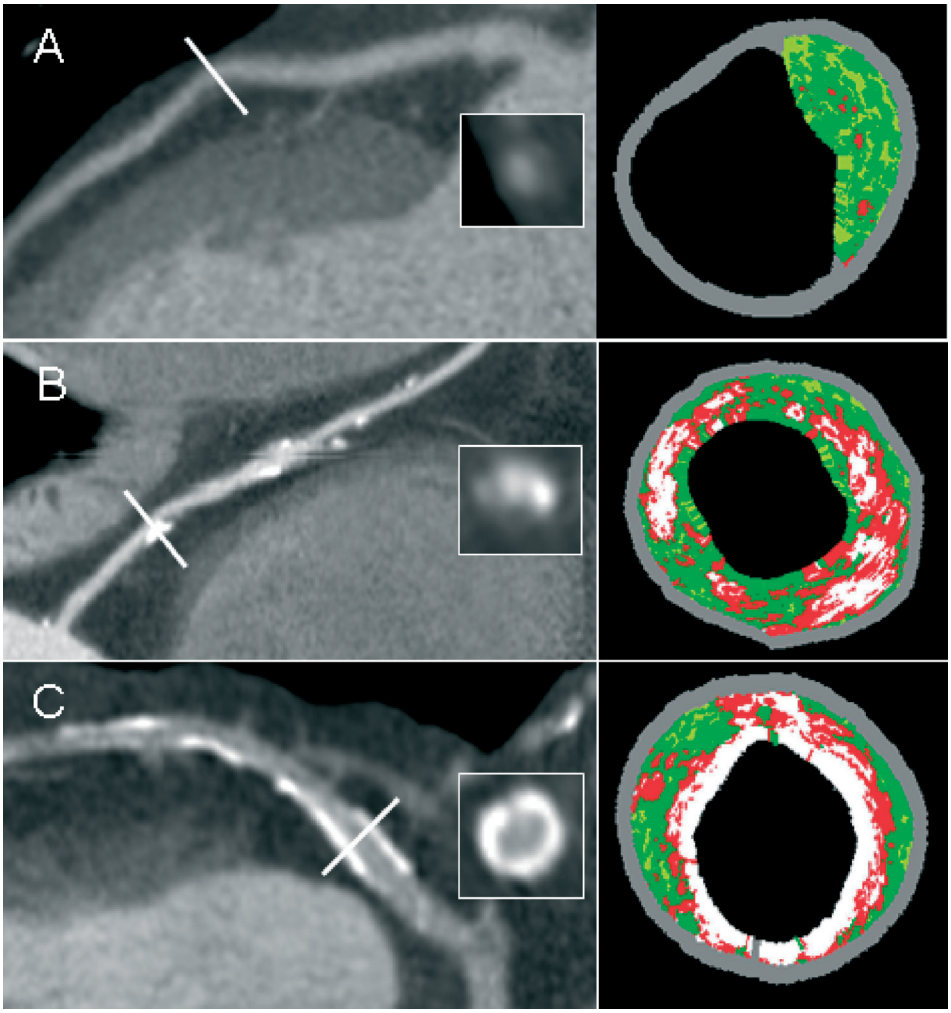

Figure 2. Example of plaque composition on MSCT and VH IVUS.
(A) Noncalcified plaque with corresponding transversal section. On VH IVUS, plaque containing predominantly fibrous and fibro-fatty tissues is demonstrated. (B) Mixed plaque with corresponding transversal section, showing the features of thin-cap fibroatheroma on VH IVUS. (C) Calcified plaque with corresponding transversal section demonstrating circular pattern of calcium accumulation. The corresponding VH IVUS image confirms the circular deposition of dense calcium in the plaque. Noncalcified tissue located behind the calcium is depicted, which is not visible on the MSCT images due to the partial volume effect of extensive calcifications. MSCT, multi-slice computed tomography; VH IVUS, virtual histology intravascular ultrasound.

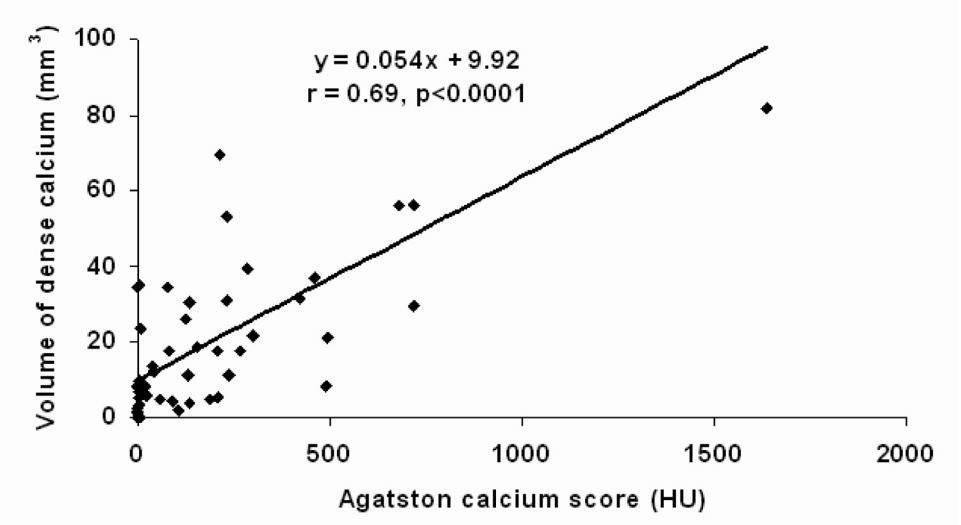

Figure 3. Correlation of Agatston score with volume of dense calcium.
Correlation of the Agatston coronary calcium score (HU) on MSCT and the volume of dense calcium (mm^3) on VH IVUS in the total of those coronary segments in which VH IVUS examination was performed. HU, Hounsfield units; MSCT, multi-slice computed tomography; VH IVUS, virtual histology intravascular ultrasound.

Results from VH IVUS are specified per plaque type in Table 2 and Figure 4. No differences were observed in lesion length. Noncalcified plaques contained significantly more fibrotic and fibro-fatty tissues as compared with calcified plaques (60.90±9.21% versus 54.60±8.33%, p=0.001, and 28.11±13.03% versus 21.37±9.75%, p=0.006, respectively).

Table 2. Coronary plaque characteristics on VH IVUS in three types of plaques on MSCT

VH IVUS characteristics	Non-calcified plaques (n=48)	Mixed plaques (n=71)	Calcified plaques (n=49)	p-value
Lesion length (mm)	22.33±14.55	19.53±12.48	21.51±16.30	0.55
Fibrotic (%)	60.90±9.21	57.22±8.31	54.60±8.33	0.002
Fibro-Fatty (%)	28.11±13.03	23.95±9.37	21.37±9.75	0.008
Necrotic Core (%)	8.31±5.50	11.22±5.65	13.85±6.32	<0.0001
Dense Calcium (%)	2.68±3.01	7.61±8.94	10.18±6.71	<0.0001
TCFA	6 (13%)	23 (32%)	4 (8%)	0.002

Data are presented as mean±SD or n (%).
MSCT, multi-slice computed tomography; TCFA, thin cap fibroatheroma; VH IVUS, virtual histology intravascular ultrasound.

Mixed and calcified plaques showed more dense calcium on VH IVUS as compared with noncalcified plaques (7.61±8.94% versus 2.68±3.01%, p=0.001, and 10.18±6.71% versus 2.68±3.01%, p<0.0001, respectively). More necrotic core tissue was observed in mixed and calcified plaques as compared with noncalcified plaques (11.22±5.65% versus 8.31±5.50%, p=0.02, and 13.85±6.32% versus 8.31±5.50%, p<0.0001, respectively).

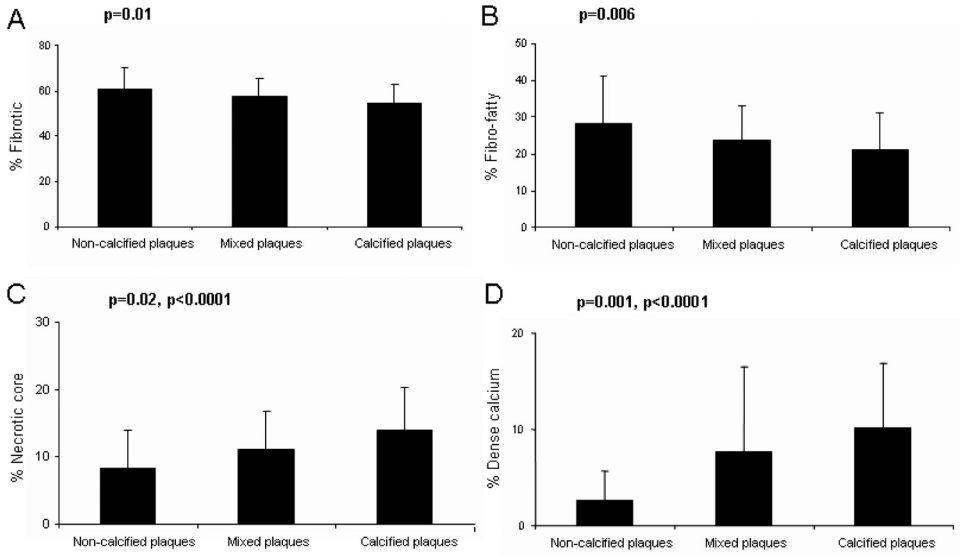

Figure 4. Differences in coronary plaque composition on VH IVUS between noncalcified, mixed, and calcified plaques on MSCT.

Significantly more fibrotic and fibro-fatty tissues were demonstrated in noncalcified plaques as compared with calcified plaques (A, B). Mixed and calcified plaques contained significantly more necrotic core tissue and dense calcium on VH IVUS as compared with noncalcified plaques (C, D). MSCT, multi-slice computed tomography; VH IVUS, virtual histology intravascular ultrasound.

Prevalence of TCFA in 3 types of plaques on MSCT

Regarding the VH IVUS qualitative assessment, TCFAs were most frequently observed in mixed plaques as compared with noncalcified and calcified plaques (Table 2, Figure 5). Twenty-three (32%) of mixed plaques fulfilled the TCFA criteria on VH IVUS as compared with only 6 (13%) in noncalcified and 4 (8%) in calcified plaques (p=0.002).

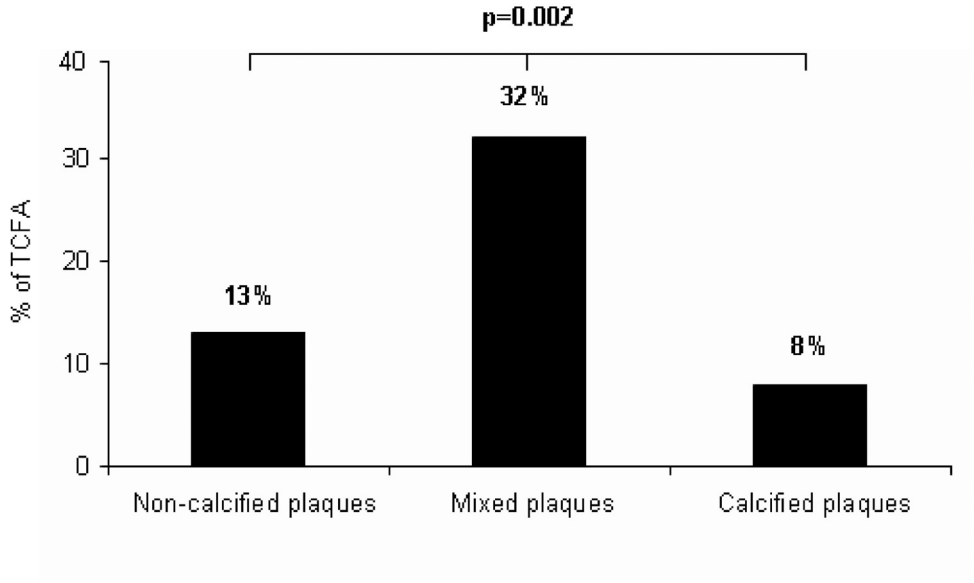

Figure 5. Prevalence of TCFAs in the 3 types of plaques on MSCT.
Thin-cap fibroatheromas (TCFAs) were significantly more prevalent in mixed plaques as compared with noncalcified and calcified plaques. TCFA, thin cap fibroatheroma.

Discussion

The findings of the present study demonstrated a good correlation between plaque composition on MSCT and VH IVUS. Coronary calcium score with MSCT showed a significant correlation with dense calcium volume measurements on VH IVUS. Similarly, only a very limited amount of dense calcium was observed in noncalcified plaques on MSCT, whereas increasingly more dense calcium on VH IVUS was demonstrated in mixed and calcified plaques. At the same time, calcified and mixed plaques contained increasingly less fibrotic and fibro-fatty tissues as compared with noncalcified plaques. However, VH IVUS with superior spatial resolution allowed a more precise evaluation of

plaque composition as compared with MSCT. Calcified plaques on MSCT were shown to contain a considerable amount of noncalcified tissue on VH IVUS. Plaques deemed to be completely noncalcified on MSCT, on the other hand, still contained some small amount of calcium, albeit only very limited. Also, distinction between fibrous and fibro-fatty tissue may not be feasible using MSCT. Finally, of particular interest was the observation that TCFAs were most prevalent in mixed plaques, suggesting a higher degree of vulnerability of these mixed plaques on MSCT.

Correlation of plaque composition between 2 techniques

In the present study, the Agatston calcium score on MSCT significantly correlated with the volume of dense calcium on VH IVUS. This observation is in line with previous studies comparing the Agatston calcium score obtained by electron beam computed tomography with histopathology. Indeed, Mautner et al [14] have previously demonstrated an excellent correlation between calcium score and calcium area on histologic sections of the coronary arteries ($r=0.96$, $p<0.0001$). Similarly, accurate detection of calcified plaques was demonstrated on coronary artery scanning without contrast enhancement as compared with grayscale IVUS. In a study by Baumgart et al,[15] calcium on electron beam computed tomography was detected with a sensitivity of 97% and a specificity of 80%. Moreover, our findings indicate significantly more dense calcium in mixed and calcified plaques on noninvasive coronary angiography with MSCT as compared with lesions deemed to be noncalcified on MSCT. In line with these observations, previous comparative studies with grayscale IVUS demonstrated accurate detection of plaques containing calcium on MSCT, with mixed plaques showing a sensitivity of 94%, whereas the same sensitivity was demonstrated to detect calcified plaques (94% to 95%).[1,3] Similarly, MSCT plaque density values were higher in plaques containing calcium as detected by grayscale IVUS and histopathology.[4,16] Conversely, noncalcified plaques on MSCT in our study contained significantly more fibrotic and fibro-fatty tissues as compared with calcified plaques.

However, in contrast to grayscale IVUS, VH IVUS may allow more detailed analysis of plaque composition, including the in vivo quantification of specific histologic components of noncalcified plaque tissue. Noncalcified plaques in this study contained fibrotic, fibro-fatty, and necrotic core tissues, whereas the superior spatial resolution of the technique (100 to 200 μm) as compared with MSCT (0.4 mm) also allowed the detection of minimal amounts of calcium. In addition, plaques located in coronary segments without detectable calcium on coronary calcium scoring contained small volumes of dense calcium on VH IVUS (Figure 3), highlighting the fact that minor calcifications may be missed by MSCT.

Interestingly, calcified plaques on MSCT still contained a high amount of noncalcified components on VH IVUS. This could be explained by the partial volume effect of coronary calcium that occurs during MSCT imaging. Indeed, it has been well established that the presence of high-attenuation objects, such as dense calcifications, leads to overestimation of the lesion. As a result, adjacent tissues with lower attenuation values cannot be adequately depicted in the presence of dense calcium, and remain unrecognized.[17]

Prevalence of TCFA in different plaque types

Previous histological studies have demonstrated that lesions containing a considerable amount of necrotic core tissue without evidence of an overlying fibrous cap (TCFA lesions) may be considered as a precursor of coronary plaque rupture.[18] In vivo, TCFA may be detected by VH IVUS and have indeed been more frequently observed in patients with acute coronary syndromes as compared with those with stable CAD. In a study by Rodriguez-Granillo et al,[10] nonculprit, nonobstructive lesions were examined by VH IVUS in 23 patients presenting with acute coronary syndromes and in 32 patients with stable CAD, demonstrating significantly higher incidence of TCFA in patients with acute coronary syndromes. An important finding of the present study is that TCFA were most frequently located in mixed plaques on MSCT. Accordingly, one could argue that mixed plaques might resemble high-risk lesions, because these lesions were also associated with other features of vulnerability on VH IVUS, such as an elevated amount of necrotic core tissue and less extensive calcification.[18] Moreover, in studies comparing plaque type on MSCT between patients presenting with acute coronary syndromes and stable CAD, completely calcified plaques were less prevalent in patients presenting with acute coronary syndromes.[5–7] Finally, a recent study exploring potential prognostic predictors of cardiovascular events on MSCT showed that mixed lesions were associated with adverse events on follow-up.[19] Ideally, features of TCFA would be determined on MSCT directly. Indeed, previous studies have attempted to characterize features of TCFA on MSCT.[3] In comparison to grayscale IVUS, lipid core was identified on MSCT with an accuracy of 70%.[3] Nevertheless, it is important to realize that the insufficient spatial resolution of MSCT precludes exact location of lipid accumulation in the plaque as well as visualization of the thin fibrous cap. Accordingly, direct identification of TCFA on MSCT is at present not feasible.

Study limitations

Several limitations of the study should be acknowledged. First, noninvasive and invasive examinations were performed within 1 month. Accordingly, minor changes in plaque burden and composition may have occurred. Second, no validation of lesion length or distance measurements on MSCT and IVUS was performed and differences between modalities may have affected the accuracy of our results to a minor extent. Third, VH IVUS is a relatively new technique. Therefore, more extensive validation in larger patient populations and with the different VH IVUS systems that are available remains to be seen, while also more standardized representation of VH IVUS data is needed. Fourth, no plaque density measurements were performed on MSCT as it remains uncertain whether these measurements are reproducible. Indeed, operator dependency as well as potential variations in contrast attenuation may highly influence measurements.[20] Finally, MSCT is still associated with a substantial radiation dose, and administration of contrast material is required.

Conclusions

This study demonstrated a good correlation between quantification of calcium on MSCT and VH IVUS. In addition, plaque classification on MSCT paralleled relative plaque composition on VH IVUS, although VH IVUS provided more precise plaque characterization. Mixed plaques on MSCT were associated with high-risk features on VH IVUS, which suggests that MSCT observations might be useful for risk stratification. Further studies are needed to confirm the results.

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Chapter 9

Evaluation of Plaque Characteristics in Acute Coronary Syndromes: Non-Invasive Assessment With Multi-Slice Computed Tomography and Invasive Evaluation With Intravascular Ultrasound Radiofrequency Data Analysis

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Abstract

Aims: Atherosclerotic plaque characteristics play an important role in the development of coronary events. We investigated coronary plaque characteristics on multi-slice computed tomography (MSCT) and virtual histology intravascular ultrasound (VH IVUS) in patients with acute coronary syndromes (ACS) and stable coronary artery disease (CAD).

Methods: Fifty patients (25 with ACS, 25 with stable CAD) underwent 64-slice MSCT followed by VH IVUS in 48 (96%) patients.

Results: In ACS patients, 32% of plaques were non-calcified on MSCT and 59% were mixed (corresponding odds ratio (95% CI) 3.9 (1.6-9.5), p=0.003 and 3.4 (1.6-6.9), p=0.001, respectively). In patients with stable CAD, completely calcified lesions were more prevalent (61%). On VH IVUS, the percentage of necrotic core was higher in the plaques of ACS patients (11.16±6.07% versus 9.08±4.62% in stable CAD, p=0.02). In addition, thin cap fibroatheroma were more prevalent in ACS patients (32% versus 3% in patients with stable CAD, p<0.001) and were most frequently observed in mixed plaques on MSCT. Plaque composition both on MSCT and VH IVUS was identical between culprit and non-culprit vessels of ACS patients.

Conclusions: On MSCT, differences in plaque characterization were demonstrated between patients with ACS and stable CAD. Plaques of ACS patients showed features of vulnerability to rupture on VH IVUS. Potentially, MSCT may be useful for non-invasive identification of atherosclerotic plaque patterns associated with higher risk.

Introduction

Despite improvement in medical therapy and use of novel interventional techniques, acute coronary syndromes (ACS) continue to be one of the leading causes of morbidity and mortality in developed countries.[1] In the occurrence of coronary events, atherosclerotic plaque characteristics (including degree of stenosis as well as composition) have been demonstrated to play a pivotal role. Based on pathological studies of the victims of sudden cardiac death, lesions containing a large amount of necrotic core with an overlying thin fibrous cap (referred to as thin cap fibroatheroma, TCFA) have been linked to plaque rupture.[2,3] With regard to the degree of stenosis, ACS may frequently arise from lesions with only mild to moderate stenosis since these lesions may be more common than severe obstructive lesions.[4-8]

Accordingly, in vivo detection of potentially vulnerable plaques may improve prevention of cardiovascular events. Both invasive and non-invasive techniques are currently under development. Recently, virtual histology intravascular ultrasound (VH IVUS) has been introduced. This invasive imaging modality allows in vivo quantitative evaluation of 4 coronary plaque components, namely fibrotic tissue, fibro-fatty tissue, necrotic core and dense calcium.[9] Nasu et al recently showed that VH IVUS, as compared to histopathology, allowed detection of necrotic core with an accuracy of 88.3%, whereas the accuracy to detect dense calcium was as high as 96.5%.[10] Non-invasively, plaque extent and composition may be evaluated by multi-slice computed tomography (MSCT) coronary angiography.[11-14] Previous studies have suggested that MSCT can recognize differences in coronary plaque composition with different clinical presentations,[15-18] although comparison with invasive imaging is lacking.

The purpose of the present study was to evaluate plaque characteristics in patients presenting with ACS and stable coronary artery disease (CAD) using both non-invasive MSCT and invasive VH IVUS.

Methods

Patient population and study protocol

Patients with ACS included unstable angina and non-ST-segment elevation myocardial infarction, defined according to the guidelines of the European Society of Cardiology[19] and the American College of Cardiology/American Heart Association.[20] The control group of the present study consisted of age- and gender-matched patients presenting at the out-patient clinic with stable angina pectoris and requiring conventional coronary angiography.

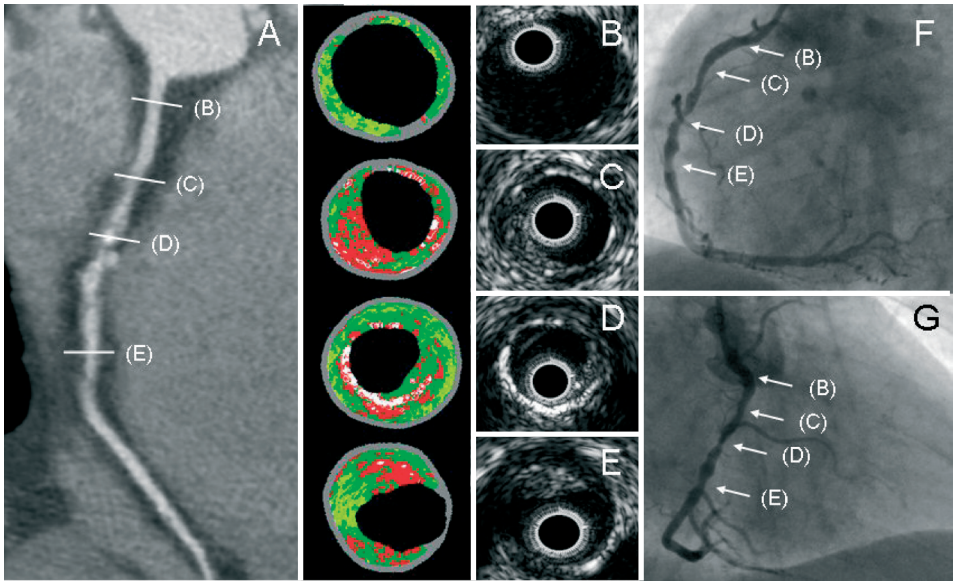

Figure 1. Coronary plaques in the culprit vessel of a patient presenting with unstable angina pectoris. Panel A, MSCT multiplanar reconstruction of the right coronary artery showing obstructive non-calcified and mixed plaques. Panels B to E, Gray-scale IVUS images and the corresponding VH IVUS images. In panel B, small amount of plaque in the proximal right coronary artery is seen, which appears normal on MSCT. TCFA with a large amount of necrotic core are detected in proximally and distally located non-calcified plaques of the right coronary artery (Panels C and E). A corresponding cross section of a mixed plaque in the mid-right coronary artery shows plaque with calcium on VH IVUS (Panel D). Multiple obstructive stenoses in the right coronary artery were confirmed on invasive coronary angiography (Panels F and G). VH IVUS plaque components: dark green indicates fibrotic tissue; light green, fibro-fatty tissue; red, necrotic core; white, dense calcium.

As part of the clinical evaluation, all patients underwent 64-slice MSCT coronary angiography, followed by invasive coronary angiography. Median interval between MSCT and invasive coronary angiography (with VH IVUS imaging during the same procedure) was 1 (range 0-2) day in patients presenting with ACS; patients with stable CAD underwent both procedures within 1 month. Patients with acute coronary events or worsening of angina between MSCT and invasive coronary angiography were excluded. Additional contraindications for MSCT were (supra-) ventricular arrhythmias, renal insufficiency (serum creatinine >120 µmol/L) and known allergy to iodine contrast media.

Exclusion criteria for IVUS were severe vessel tortuousness, severe luminal narrowing precluding insertion of IVUS catheter or vessel occlusion. In a previous study, we evaluated differences in plaque characteristics between patients with ACS and stable CAD with 16-slice MSCT.[18]

Table 1. Clinical characteristics of the study population

Characteristics	ACS (n=25)	Stable CAD (n=25)	p-value
Male gender	18 (72%)	14 (56%)	0.2
Age (yrs)	57±11	61±11	0.2
Obesity	3 (12%)	5 (20%)	0.4
Type 2 diabetes mellitus	3 (12%)	6 (24%)	0.5
Hypercholesterolemia	17 (68%)	18 (72%)	0.8
Hypertension	11 (44%)	16 (64%)	0.2
Family history of CAD	13 (52%)	12 (48%)	0.8
Smoking	14 (56%)	9 (36%)	0.2
Previous MI	4 (16%)	1 (4%)	0.4
Previous PCI	7 (28%)	2 (8%)	0.1

ACS, acute coronary syndromes; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

In this study, 22 and 24 patients with respectively ACS and stable CAD were enrolled, showing statistically significant differences in plaque characteristics on MSCT between both groups. Based on these previous findings we decided to enrol 25 patients in each group. In total, 72 patients were initially selected for inclusion in the study. However, 22 patients could eventually not be included (11 patients did not undergo MSCT prior to angiography due to logistical reasons, 8 had high heart rate and contraindications for β-blockers and 3 had severe renal dysfunction). As a consequence, 50 patients (25 presenting with ACS, 25 with stable CAD) scheduled for conventional coronary angiography were included in the study. Patient characteristics are provided in Table 1. The study protocol was approved by the ethics committee and informed consent was obtained from all patients.

MSCT

Image acquisition

MSCT examination was performed using a 64-slice Toshiba Aquilion (Toshiba Medical Systems, Tokyo, Japan) scanner. The images were acquired with a collimation of 64 x 0.5 mm and a tube rotation of 0.4 seconds. The tube current was 300 or 350 mA at 120 or 135 kV, respectively. The contrast material (Iomeron 400, Bracco, Milan, Italy) was administered in an antecubital vein at a rate of 5 ml/s and the amount of 90-105 ml depending on the total scan time. The timing of the start of the scan was performed using detection of automated peak enhancement in the descending aorta (baseline

Hounsfield units +100). Image acquisition was performed during an inspiratory breath hold of approximately 10 seconds and during electrocardiographic gating.21 If the heart rate was ≥65 beats/min additional oral β-blockers (metoprolol, 50 or 100 mg, single dose, 1 hour prior to the examination) were provided if tolerated.

Images were reconstructed in the R-R interval phase showing least motion artefacts with a slice thickness of 0.5 mm and an increment of 0.3 mm. When extensive calcifications were present, sharper reconstruction kernels were used to reduce blooming artefacts of calcium. Subsequently, images were transferred to a remote workstation for post-processing and evaluation.

Image analysis

Images were evaluated using a remote workstation with dedicated software (Vitrea 2, Vital Images, USA). Two experienced observers who were unaware of the clinical history and IVUS findings assessed MSCT angiograms side-by-side in consensus. Coronary plaques were visually evaluated on axial images and curved multiplanar reconstructions. Structures >1 mm2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding tissue were regarded as plaques.12 The location of plaques in the arteries was defined using side branches and coronary ostia as landmarks. Plaques were classified into 3 types, namely non-calcified (plaques having lower density compared with the contrast-enhanced vessel lumen without any visible calcification), calcified (plaques with predominantly high density) and mixed (plaques with non-calcified and calcified elements within the same plaque).

The left main coronary artery was considered part of the left anterior descending coronary artery and the intermediate branch was considered part of the left circumflex coronary artery.

VH IVUS

Image acquisition

For each IVUS examination, a 20 MHz, 2.9 F, phased-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, USA) was used. After administration of intracoronary nitrates, the IVUS catheter was introduced to the distal coronary artery. Using automated pullback device, the transducer was withdrawn at a continuous speed of 0.5 mm/s up to the coronary ostium. Cine runs before and during contrast injection were performed to define the starting position of the IVUS catheter. Image acquisition was carefully monitored for gating or IVUS catheter pullback disturbances. The electrocardiographically triggered IVUS radiofrequency signals were acquired and stored for off-line analysis.

Image analysis

Off-line VH IVUS analyses were performed using dedicated software (pcVH 2.1, Volcano Corporation, Rancho Cordova, California, USA) by 2 experienced observers blinded to baseline patient characteristics. The location of coronary plaques (detected on MSCT) was identified using side branches and coronary ostia as landmarks. The repeated frames due to non-continuous pullback of the IVUS catheter were excluded from analysis. When drawing the lumen contours, the presence of thrombus was visually assessed, and if present, not included as plaque. For each region of interest, relative compositional quantitative plaque parameters were obtained. Four tissues were differentiated including fibrotic tissue being labelled in dark green, fibro-fatty in light green, necrotic core in red and dense calcium in white (Figure 1). In addition, the presence of IVUS derived TCFA was evaluated, which was defined as a lesion fulfilling the following criteria: 1) plaque burden >40%, 2) the presence of confluent necrotic core of >10% and 3) no evidence of an overlying fibrous cap (Figure 1), as previously described by Rodriguez-Granillo et al.[3,22-23]

Definition of the region of interest on MSCT and VH IVUS

The average of 4 plaque components on VH IVUS was calculated in the full length of plaques observed on MSCT. To ensure that identical plaques were assessed by MSCT and VH IVUS, coronary ostia and side branches were used as landmarks and distances from the landmarks to the target lesions were measured. The distances were measured on curved multiplanar reconstructions of the coronary arteries on MSCT. On IVUS, the corresponding plaque was identified using longitudinally reconstructed IVUS datasets.[12] The transversal IVUS sections were further inspected and the start and finish frames of the lesions were depicted on electrocardiographically triggered IVUS datasets.

Statistical analysis

Initial analyses were performed on a coronary plaque level. Coronary plaque characteristics on MSCT and VH IVUS were compared between patients presenting with ACS and stable CAD. Continuous variables with normal distribution were expressed as means (with standard deviation) and compared with the t-test for independent samples. When not normally distributed, continuous variables were expressed as medians (with interquartile range) and compared using the nonparametric Mann-Whitney test. Categorical variables were expressed as numbers (with percentages) and compared between groups with Chi-square test or Fisher's exact test. To account for possible interdependencies between multiple plaques within a patient, differences

in plaque composition between patients presenting with ACS and stable CAD were evaluated by logistic regression analysis with the application of generalized estimating equation method.[24] Odds ratios and 95% confidence intervals were reported.

In addition, plaque characteristics were compared between culprit and non-culprit vessels of ACS patients. Culprit vessels were defined as vessels containing the culprit lesion. The latter was identified by angiographic lesion morphology (as determined on conventional coronary angiograms), ECG findings and/or regional wall motion abnormalities on left ventriculography or echocardiography.[6] Continuous variables with normal distribution were expressed as means (with standard deviation) and compared with the t-test for independent samples. When not normally distributed, continuous variables were expressed as medians (with interquartile range) and compared using the nonparametric Mann-Whitney test. Categorical variables were expressed as numbers (with percentages) and compared between groups with Chi-square test. To account for possible interdependencies between multiple plaques within a patient, differences in plaque composition between culprit and non-culprit vessels were evaluated by logistic regression analysis with the application of generalized estimating equation method.

Table 2. Correlation between baseline patient characteristics and clinical presentation with ACS

MSCT parameter	Univariable	
	OR (95% CI)	p-value
Age	1.0 (0.97-1.1)	0.2
Male gender	2.0 (0.6-6.6)	0.2
Obesity	1.8 (0.4-8.7)	0.4
Type 2 diabetes mellitus	2.3 (0.5-10.5)	0.3
Hypercholesterolemia	1.2 (0.4-4.1)	0.8
Hypertension	2.3 (0.7-7.0)	0.09
Family history of CAD	0.9 (0.3-2.6)	0.8
Smoking	0.4 (0.1-1.4)	0.2
Previous MI	0.2 (0.02-2.1)	0.2
Previous PCI	0.2 (0.4-1.2)	0.08
Use of statins	1.7 (0.5-5.3)	0.4

ACS, acute coronary syndromes; CAD, coronary artery disease; CI, confidence intervals; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

Differences between plaque characteristics between patients presenting with ACS and stable CAD were also evaluated on a patient level. For this purpose, univariable analysis followed by multivariable logistic regression analysis was performed. The linearity assumption

for all continuous variables (age, number of non-calcified, mixed and calcified plaques, mean percentage of fibrotic, fibro-fatty tissues, necrotic core and dense calcium as well as number of TCFA per patient) was assessed as follows: first, continuous variables were divided into meaningful subgroups. Subsequently, the log odds were calculated for each subgroup and plotted against the midpoint. The assumption of linearity was satisfied as a stepwise change in the odds was observed when moving between the adjacent categories of each variable. The final multivariable analysis model included baseline characteristics showing correlation at a significance level of $p<0.1$ in the univariable analysis (the presence of hypertension and the history of previous percutaneous coronary intervention, Table 2). In addition, since plaque observations are influenced by patient age and gender, age and gender were included as covariates of the multivariable analysis regardless of the significance level of correlation in the univariable analysis.

All analyses were 2-tailed and p-values <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS (version 12.0, SPSS Inc, Chicago, Ill, USA) and SAS (release 6.12, SAS institute, Cary, NC, USA) software.

Results

Patient characteristics

Baseline characteristics of patients presenting with ACS and stable CAD are provided in Table 1. No differences were observed in the prevalence of CAD risk factors and the use of medication between the 2 patient groups. All ACS patients presented with chest pain and ECG abnormalities, whereas troponin levels were elevated in 6 (24%) patients.

Table 3. Correlation of coronary plaque composition on MSCT with clinical presentation with ACS as compared to stable CAD: plaque level logistic regression analysis with the application of generalized estimating equation method

Plaque characteristics	ACS (plaque n=179)	Stable CAD (plaque n=118)	OR (95% CI)	p-value*
Number of non-calcified plaques	57 (32%)	14 (12%)	3.9 (1.6-9.5)	0.003
Number of mixed plaques	105 (59%)	32 (27%)	3.4 (1.6-6.9)	0.001
Number of calcified plaques	17 (9%)	72 (61%)	0.06 (0.02-0.2)	<0.001

*p-value refers to logistic regression analysis with the application of generalized estimating equation method.
ACS, acute coronary syndromes; CAD, coronary artery disease; CI, confidence intervals; MSCT, multi-slice computed tomography; OR, odds ratio.

Plaque characteristics in patients with ACS versus stable CAD

MSCT. Non-invasive MSCT angiograms of all patients were of diagnostic image quality and were included in the analysis. Coronary plaques were detected in all 50 patients and in 150 vessels (75 vessels in ACS patients and 75 vessels in patients with stable CAD). In total, 179 and 118 plaques were observed in patients with ACS and stable CAD, respectively. In general, more plaques were observed in ACS patients (median 7 plaques, range 5-10) as compared to patients with stable CAD (median 5 plaques, range 2-7, p=0.04). Non-obstructive plaques were more prevalent in ACS patients as compared to patients with stable CAD (median 5, range 3-7 versus median 3, range 2-5, p=0.03). No difference in the number of obstructive plaques was observed (median 2, range 0-4 in ACS patients versus median 0, range 0-3 in patients with stable CAD, p=0.2).

Table 4. Correlation of coronary plaque composition on MSCT with clinical presentation with ACS: patient level analysis (with the relations adjusted for age, gender, the presence of hypertension and the history of previous percutaneous coronary intervention)

MSCT parameter	Multivariable	
	OR (95% CI)	p-value
Number of non-calcified plaques	2.2 (1.3-3.9)	0.006
Number of mixed plaques	1.9 (1.2-3.0)	0.004
Number of calcified plaques	0.5 (0.3-0.8)	0.005

ACS, acute coronary syndromes; CI, confidence intervals; OR, odds ratio.

The findings on coronary plaque composition on MSCT in patients presenting with ACS versus stable CAD are presented in Tables 3 and 4. Relatively more plaques in patients presenting with ACS were either non-calcified or mixed (corresponding odds ratio (OR) 3.9, p=0.003 and 3.4, p=0.001, respectively). In contrast, lesions were less frequently calcified (corresponding OR 0.06, p<0.001) (Table 3). To account for within patient correlations, analysis was performed on a patient level using multivariable analysis. As shown in Table 4, the correlation between the clinical presentation with ACS and the increasing number of non-calcified and mixed plaques as well as a lower number of calcified plaques remained significant on a patient level.

VH IVUS: quantitative evaluation. VH IVUS was successfully performed in 48 (96%) patients (including 23 patients with ACS and 25 with stable CAD) and in 103 vessels (50 vessels in ACS patients, 53 vessels in patients with stable CAD). VH IVUS was not performed in 2 patients due to severely obstructive disease in the proximal coronary

segments. In total, IVUS was available in 97 coronary plaques of patients with ACS and 61 plaques of patients with stable CAD. An example of plaque composition on MSCT with the corresponding VH IVUS images is provided in Figure 1.

No differences were observed in the amount of fibrotic tissue (59.37±7.73% versus 56.73±10.1%, p=0.07), fibro-fatty tissue (23.92±10.15% versus 27.11±11.36%, p=0.07) and the amount of dense calcium (5.55±5.13% versus 7.09±9.28%, p=0.18) in plaques of the 2 patient populations. The amount of necrotic core, however, was larger in plaques of patients with ACS (11.16±6.07% versus 9.08±4.62%, p=0.02) (Figure 2 A). No correlation between plaque components and clinical presentation with ACS was observed when analysis was performed on a patient level (Table 5).

Table 5. Correlation of coronary plaque composition on VH IVUS with clinical presentation with ACS: patient level analysis (with the relations adjusted for age, gender, the presence of hypertension and the history of previous percutaneous coronary intervention)

MSCT parameter	Multivariable	
	OR (95% CI)	p-value
Percentage of fibrotic tissue	1.1 (1.0-1.2)	0.3
Percentage of fibro-fatty tissue	1.0 (0.9-1.1)	0.5
Percentage of necrotic core	1.1 (0.9-1.2)	0.5
Percentage of dense calcium	0.9 (0.7-1.1)	0.3
Number of TCFA	12.0 (1.7-85.6)	0.01

ACS, acute coronary syndromes; CI, confidence intervals, OR, odds ratio.

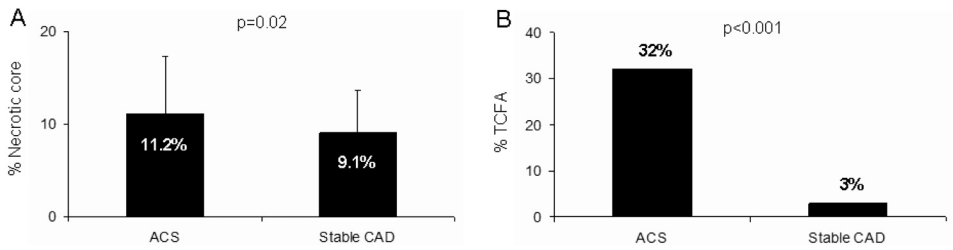

Figure 2. The amount of necrotic core and prevalence of TCFA in plaques of patients presenting with ACS and with stable CAD. Panel A, A larger amount of necrotic core was observed in plaques of patients with ACS as compared to patients with stable CAD. Panel B, TCFA were more frequently observed in plaques of patients with ACS as compared to patients with stable CAD.

VH IVUS: qualitative evaluation. Qualitative evaluation of coronary plaques showed the presence of TCFA in 31 of 97 (32%) plaques of patients with ACS, whereas only 2 of 61 (3%) plaques of patients with stable CAD had features of TCFA (p<0.001) (Figure 2 B). When data were analyzed on a patient level, this correlation between an increased number of TCFA and clinical presentation with ACS remained (Table 5). In ACS patients, VH IVUS derived TCFA were most frequently observed in lesions classified as mixed (68%) on MSCT as compared to non-calcified (19%) and calcified plaques (13%, p=0.001) on MSCT. All TCFA were located in mixed plaques of patients with stable CAD (100%).

Plaque characteristics in culprit vessels versus non-culprit vessels

MSCT. In ACS patients, 25 culprit and 50 non-culprit vessels were analyzed. In total, 72 plaques were observed in culprit arteries and 107 in non-culprit arteries. The median number of plaques in culprit vessels was slightly higher as compared to non-culprit vessels (median 3 plaques, range 2-4 versus median 2 plaques, range 1-4, p=0.06, respectively). Concerning plaque composition, no differences in the distribution of plaque types were observed between culprit and non-culprit vessels (Table 6). Both in culprit and non-culprit vessels, mixed plaques were noted most often, followed by non-calcified plaques, whereas calcified plaques had the lowest prevalence.

Table 6. Correlation of coronary plaque composition on MSCT with plaque localization in culprit vessels as compared to non-culprit vessels of patients with ACS: plaque level logistic regression analysis with the application of generalized estimating equation method

Plaque characteristics	Culprit vessels (plaque n=72)	Non-culprit vessels (plaque n=107)	OR (95% CI)	p-value*
Number of non-calcified plaques	19 (26%)	38 (36%)	0.6 (0.3-1.2)	0.2
Number of mixed plaques	44 (61%)	61 (57%)	1.2 (0.6-2.2)	0.6
Number of calcified plaques	9 (13%)	8 (7%)	1.8 (0.6-5.3)	0.3

*p-value refers to logistic regression analysis with the application of generalized estimating equation method.

ACS, acute coronary syndromes; CI, confidence intervals; MSCT, multi-slice computed tomography; OR, odds ratio.

VH IVUS: quantitative evaluation. VH IVUS was performed in 19 culprit and 31 non-culprit vessels of ACS patients. In total, 39 plaques were located in culprit arteries and 58 plaques in non-culprit arteries. Similar to MSCT, no differences were observed between plaque composition in culprit and non-culprit arteries on VH IVUS. Plaques of the 2 groups

of arteries showed no differences in the amount of fibrotic tissue (57.99±6.95% versus 60.3±8.13%, p=0.15), fibro-fatty tissue (26.3±10.23% versus 22.32±9.86%, p=0.06) and dense calcium (5.35±4.86% versus 5.69±5.35%, p=0.75). Of interest, no difference was demonstrated in the amount of necrotic core either (10.36±5.62% versus 11.69±6.35%, p=0.29) (see Figure 3A).

VH IVUS: qualitative evaluation. Importantly, the proportion of TCFA was similar in plaques of culprit and non-culprit arteries (26% versus 36%, p=0.27) (Figure 3B). In culprit vessels, plaques having features of TCFA were most frequently observed in mixed plaques (50%) as compared to non-calcified (20%) and calcified plaques (30%, p=0.006) on MSCT. This proportion was similar also in non-culprit vessels, where TCFA was observed in 76% of mixed plaques, 19% of non-calcified and 5% of calcified plaques (p=0.007) on MSCT.

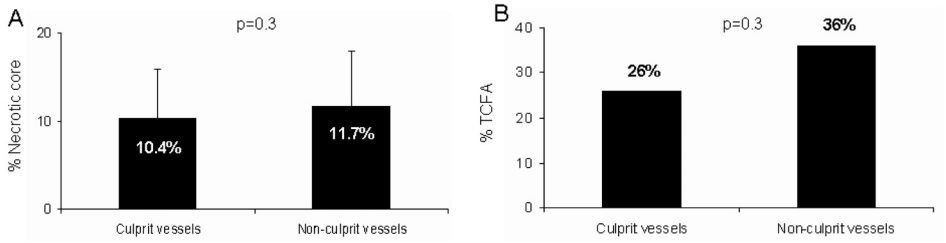

Figure 3. The amount of necrotic core and prevalence of TCFA in plaques located in culprit and non-culprit vessels of patients with ACS. Panel A, Plaques located in culprit and non-culprit vessels contained identical amount of necrotic core. Panel B, The proportion of plaques having features of TCFA on VH IVUS was identical in culprit and non-culprit vessels.

Discussion

The findings of coronary plaque characterization using MSCT angiography and VH IVUS may be summarized as follows. First, the proportion of completely calcified plaques on MSCT was lower in patients with ACS, while non-calcified and mixed plaques were more prevalent as compared to patients with stable CAD. This observation corresponded with a larger amount of necrotic core and a higher prevalence of TCFA on VH IVUS in the plaques of ACS patients.

Second, multiple non-calcified and mixed plaques on MSCT were observed in both culprit and non-culprit vessels of patients presenting with ACS. No differences in plaque composition between non-culprit and culprit vessels were observed on VH IVUS.

Of interest, TCFA as detected by VH IVUS were most frequently observed in mixed plaques on MSCT.

Differences in plaque composition between ACS patients and patients with stable CAD

In the present study, MSCT revealed more diffuse CAD and more non-calcified and mixed plaques in patients with ACS as compared to patients with stable CAD. A higher prevalence of less calcified plaques on MSCT in ACS patients was also reported by Hoffmann et al who compared 14 patients with ACS to 9 patients with stable CAD.[17] Other studies have reported similar observations.[15-18] However, these investigations lacked validation against invasive plaque imaging, although dedicated gray-scale IVUS studies have shown comparable results.[25]

Important features of plaque vulnerability may include a large amount of necrotic core and the presence of TCFA, as demonstrated in previous pathological studies.[2,3] Also in the present study, increased necrotic core was demonstrated with VH IVUS in the plaques of patients with ACS as compared to patients with stable CAD. In addition, 94% of the identified TCFA were observed in ACS patients.

Interestingly, completely calcified plaques on MSCT were more prevalent in patients with stable CAD, although the amount of calcium on VH IVUS was similar between the 2 groups. A possible explanation may be the fact that calcium in comparison to non-calcified tissue is generally overestimated on MSCT.[14] A more likely explanation, however, may be the fact that ACS in the present study was associated with a higher number of coronary plaques. Moreover, these lesions were often classified as mixed (containing both non-calcified and calcified tissues) on MSCT. Thus, although the total amount of calcium was similar on VH IVUS, more plaques that also contained non-calcified tissue were observed on MSCT in ACS patients. This observation may have implications for calcium scoring. Indeed, among individual patients, similar calcium scores may correspond to considerably different degrees of non-calcified tissue. Accordingly, the presence of relatively more mixed plaques as compared to calcified plaques may be associated with increased risk[26] but is not appreciated if only calcium scoring is performed.

Plaque composition in culprit and non-culprit vessels

Another important finding of the study is that both invasive and non-invasive imaging showed similar plaque features in culprit and non-culprit vessels. On MSCT, lesions in ACS tended to be equally distributed, as reflected by a similar number of lesions per vessel and similar plaque composition in 2 types of vessels. On VH IVUS this observation was paralleled by a similar amount of necrotic core and an equal distribution of TCFA. The observation that plaques with features of vulnerability also occur in non-culprit vessels is in-line with previous studies using

invasive coronary angiography, gray-scale and VH IVUS.[22,27-29] Recently, Rodriguez-Granillo and colleagues also reported a larger proportion of necrotic core even in non-culprit vessels of ACS patients as compared to stable CAD patients.[27] In addition, a higher prevalence of TCFA in non-culprit vessels as compared to vessels of patients with stable CAD has been demonstrated.[22] In line with these findings, elevated levels of inflammatory markers have been observed in ACS patients, reflecting the presence of generalized inflammation which may result in the development of multiple unstable coronary lesions in the entire coronary tree.[30,31] These observations further support the hypothesis of a pan-coronary distribution of potentially vulnerable plaques in patients with ACS, which may lead to recurrent events within months following the initial presentation of CAD in this population.[27,32-34]

Mixed plaques on MSCT versus TCFA on VH IVUS

Interestingly, TCFA were most frequently detected on VH IVUS in plaques that were classified as mixed on MSCT. Indeed, as previously suggested, lesions containing smaller calcium deposits (which are classified as mixed or non-calcified lesions on MSCT) may be more prevalent in ACS patients and could suggest plaque vulnerability.[25,35-37] Ehara et al compared patients with acute myocardial infarction or unstable angina to patients with stable CAD using gray-scale IVUS, and demonstrated more plaques with small calcium deposits as the culprit lesions in ACS patients.[35] Similarly, a higher prevalence of these so-called spotty calcifications has recently been reported on MSCT.[38] Accordingly, it has been suggested that mixed plaques may represent vulnerable plaques on MSCT.

Clinical implications

While risk stratification is currently based on clinical data, plaque characterization on non-invasive MSCT coronary angiography could be of use. In the present study, differences in coronary plaque patterns were demonstrated between ACS patients and patients with stable CAD. The presence of high-risk features was observed in these plaques on VH IVUS. Accordingly, MSCT may allow recognition of atherosclerotic plaque patterns representing relatively higher risk. Initial follow-up data have recently become available and have demonstrated the independent prognostic value of MSCT observations over baseline patient clinical characteristics.[26,39] However, prognostic data of plaque composition on MSCT are scarce[26] and larger outcome studies are highly needed. Patients with lower risk should be addressed in particular, since these patients would benefit most from non-invasive risk stratification with MSCT. Due to lack of prospective data, however, current guidelines do not recommend evaluation of coronary plaques for risk stratification.[40] VH IVUS on the contrary may be useful to evaluate individual plaques in patients

with higher risk. Indeed, whereas gray-scale IVUS is suboptimal in assessment of vulnerable plaque,[41] VH IVUS may potentially allow better detection of features associated with future plaque rupture. Accordingly, the technique may be useful for individualized risk assessment and permit identification of patients who may benefit from aggressive medical therapy.[42] Large prospective studies however are awaited.

Limitations

Some limitations of the study should be acknowledged. The findings of the study are based on a relatively small patient population and further studies in larger patient cohorts are needed. The study provides observational data and follow-up data were not available. In addition, only visual assessment of plaque composition on MSCT was performed and plaque density was not measured. Indeed, it remains uncertain whether these measurements are reproducible since variations in contrast attenuation as well as scan settings may highly influence the results.[43,44]

Concerning MSCT in general, the technique is still associated with intravenous contrast administration and a high radiation dose. However, substantial effort is invested in dose reduction strategies. Accordingly, the radiation exposure is expected to decrease in the near future. Indeed, considerable dose reduction was recently reported using a prospective gating protocol that allowed the acquisition of high-quality images with an average radiation dose as low as 2.1 mSv.[45]

An important limitation of VH IVUS is the fact that the technique is relatively new and not yet widely available. Accordingly, the current observations need confirmation in future studies. Moreover, the currently used 20 MHz and 30 MHz IVUS catheters allow longitudinal resolution of approximately 250 μm while the use of 40 MHz IVUS catheters would potentially improve spatial resolution of VH IVUS.[46]

Finally, intra- and inter-observer variability of MSCT and VH IVUS was not evaluated in the present study, as good agreement has been reported previously for both techniques.[14,47,48]

Conclusions

More plaques containing non-calcified tissue were observed on MSCT in ACS patients as compared to patients with stable CAD. On VH IVUS, these observations were paralleled with a higher prevalence of TCFA in plaques of ACS patients. Moreover, both techniques showed similar findings in culprit and non-culprit vessels of ACS patients, suggesting diffuse inflammation. Features of high risk on VH IVUS were most frequently observed in mixed plaques on MSCT. Potentially, MSCT may be useful for non-invasive identification of atherosclerotic plaque patterns associated with higher risk, although prospective studies in patients with lower risk are needed to confirm these observations.

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Chapter 10

Noninvasive Assessment of Plaque Characteristics With Multislice Computed Tomography Coronary Angiography in Symptomatic Diabetic Patients

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Abstract

Aims: Cardiovascular events are high in patients with type 2 diabetes while their risk stratification is more difficult. The higher risk may be related to differences in coronary plaque burden and composition. The purpose of the study was to evaluate whether differences in the extent and composition of coronary plaques in patients with and without diabetes can be observed using MSCT.

Methods: MSCT was performed in 215 patients (86, 40% with type 2 diabetes). The number of diseased coronary segments was determined per patient; each diseased segment was classified as showing obstructive (≥50% luminal narrowing) disease or not. In addition, plaque type (non-calcified, mixed and calcified) was determined. Plaque characteristics were compared in patients with and without diabetes. Regression analysis was performed to assess correlation between plaque characteristics and diabetes.

Results: Patients with diabetes showed significantly more diseased coronary segments compared to non-diabetic patients (4.9±3.5 versus 3.9±3.2, p=0.03) with more non-obstructive (3.7±3.0 versus 2.7±2.4, p=0.008) plaques. Relatively more non-calcified (28% versus 19%), calcified (49% versus 43%) and less mixed (23% versus 38%) plaques were observed in diabetes (p<0.0001). Diabetes correlated with the number of diseased segments, non-obstructive, non-calcified and calcified plaques.

Conclusions: Differences in coronary plaque characteristics on MSCT were observed between patients with and without diabetes. Diabetes was associated with higher coronary plaque burden. More non-calcified and calcified plaques while less mixed plaques were observed in diabetic patients. Thus, MSCT may be used to identify differences in coronary plaque burden, which may be useful for risk stratification.

Introduction

At present, 200 million people have diabetes mellitus worldwide while its prevalence is expected to continue increasing exponentially.[1] A close relationship between type 2 diabetes and the development of coronary artery disease (CAD) exists and[2] cardiovascular disease is the main cause of death in this patient population.[3]

Non-invasive testing, including myocardial perfusion scintigraphy and dobutamine stress-echocardiography, has been used to detect CAD in diabetic patients[4,5] and a clear association between abnormal test results and worse outcome has been demonstrated similar to the general population.[6] Nonetheless, after normal findings, still elevated event rates are observed in diabetic patients as compared to non-diabetic individuals,[6,7] indicating a need for further refinement of prognostification in this population. The higher event rates in patients with diabetes as compared to patients without diabetes could be related to differences in coronary plaque burden and composition. Therefore, direct visualization of coronary plaque burden could be a useful tool for risk stratification. Indeed, using invasive techniques, a considerably higher extent of CAD and plaque burden has been demonstrated in the presence of diabetes.[8,9]

To date, atherosclerosis has been non-invasively assessed in patients with type 2 diabetes using coronary calcium scoring revealing extensive atherosclerosis.[10,11] Still, coronary calcium scoring may seriously underestimate coronary plaque burden as non-calcified lesions are not recognized.[12] More recently, contrast-enhanced multi-slice computed tomography (MSCT) coronary angiography has become available which allows, in contrast to calcium scoring, detection of both calcified and non-calcified coronary lesions.[13-16] As a result, the technique potentially allows a more precise non-invasive evaluation of coronary atherosclerosis, which in turn could be valuable for improving risk stratification. Accordingly, the purpose of the present study was to evaluate whether differences in the extent and composition of coronary plaques in patients with diabetes as compared to patients without diabetes can be observed with MSCT.

Methods

The study population consisted of 86 (40%) patients with known type 2 diabetes mellitus and 129 (60%) patients without diabetes mellitus who underwent examination with MSCT coronary angiography for recurrent chest pain complaints. Fifty-one (24%) patients were examined with 16-slice MSCT scanner, while the majority (164, 76%) underwent examination with 64-slice MSCT. Diabetes was diagnosed according to the criteria set by

American Diabetes Association:[17] 1) symptoms of diabetes and casual plasma glucose level of ≥11.1 mmol/l or 2) fasting plasma glucose level of ≥7.0 mmol/l. Only patients in sinus rhythm, without contraindications to MSCT were included.[18] All patients gave written informed consent to the study protocol, which was approved by local ethics committee.

MSCT data acquisition

All examinations were performed using Toshiba Multi-slice Aquilion systems (Toshiba Medical Systems, Tokyo, Japan). First, a prospective coronary calcium scan without contrast enhancement was performed, followed by 16- or 64-slice MSCT coronary angiography performed according to the protocols described elsewhere.[19,20] If the heart rate was ≥65 beats/min additional oral β-blockers (metoprolol, 50 or 100 mg, single dose, 1 hour prior to the examination) were provided if tolerated.

MSCT data analysis

Coronary artery calcium score

Coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU. Total Agatston score was recorded for each patient.

Coronary plaque assessment

MSCT angiograms were evaluated by two experienced observers who were unaware of the clinical history of the patients. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification.[21] The presence of coronary plaques was visually evaluated using axial images and curved multiplanar reconstructions. One coronary plaque was assigned per coronary segment. Plaques were classified as obstructive and non-obstructive using a 50% threshold of luminal narrowing. As shown in Figure 1, three types of plaques were identified: 1. non-calcified plaques=plaques having lower density compared with the contrast-enhanced vessel lumen, 2. calcified plaques=plaques with high density and 3. mixed plaques=plaques with non-calcified and calcified elements within a single plaque. The presence of coronary plaques on MSCT, the presence of obstructive CAD in general and if located in left main (LM)/left anterior descending (LAD) coronary artery as well as the presence of obstructive CAD in one vessel (single vessel disease) or two or three vessels (multi-vessel disease) were evaluated. For each patient, the number of diseased coronary segments (segments containing plaques or previously implanted stents), the number of coronary segments with non-obstructive as well as obstructive plaques were determined. Also, the number of segments with respectively non-calcified, mixed and calcified plaques was determined.

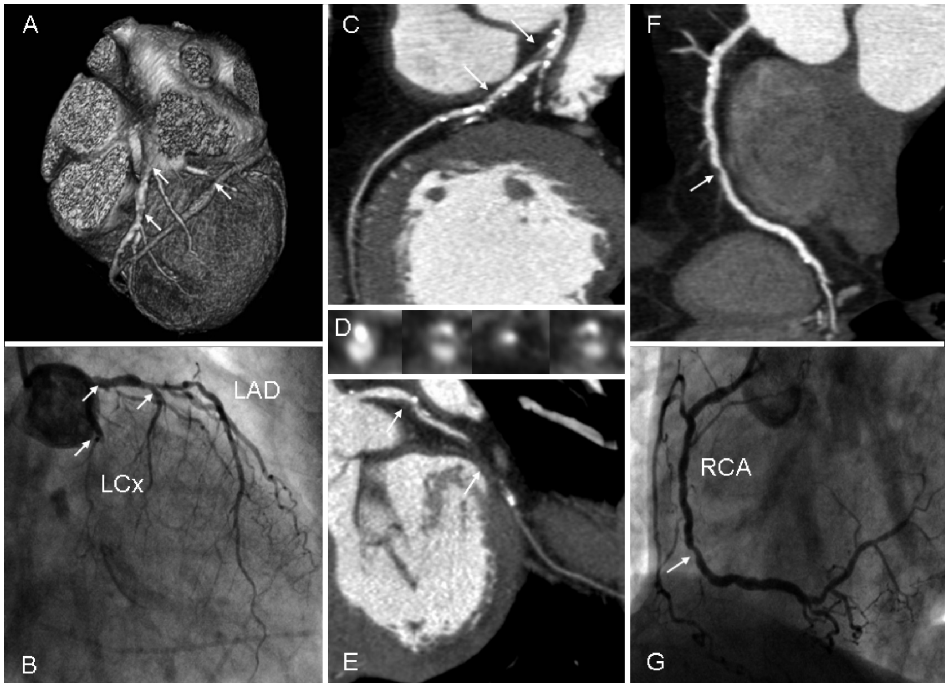

Figure 1. An example of diffuse atherosclerosis demonstrated on MSCT coronary angiography in a patient with type 2 diabetes. Three-dimensional volume rendered reconstruction depicts severe narrowing of the proximal and mid- left anterior descending coronary artery (LAD) and occluded left circumflex coronary artery (LCx) (A). The findings were confirmed by conventional coronary angiography (B). Curved multiplanar reconstruction and the corresponding transversal sections of the LAD show multiple obstructive mixed plaques in the whole course of the artery (C, D). A non-obstructive plaque followed by vessel occlusion was demonstrated in the LCx coronary artery (E). Diffuse non-obstructive calcified plaque and an obstructive non-calcified plaque were seen in the right coronary artery (RCA) (F), which was confirmed by conventional coronary angiography (G).

Statistical analysis

Categorical variables were expressed as numbers (percentages) and compared between groups with Chi-square test. Continuous variables were expressed as mean (standard deviation) and compared with the two-tailed t-test for independent samples. When not normally distributed, continuous variables were expressed as medians (interquartile range) and compared using nonparametric Mann-Whitney test.

To determine the relationship between plaque characteristics and the presence of diabetes linear regression analysis was performed when dependent variable was continuous and logistic regression analysis was performed when dependent variable was categorical. First univariate analysis was performed, followed by multivariate analysis with correction for the following variables: age, gender, risk factors for CAD, clinical presentation

(typical angina pectoris or atypical chest pain together with the presence of multiple CAD risk factors) and use of statins.

P-values <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA) and SAS software (The SAS system, release 6.12, Cary, NC, USA: SAS Institute Inc.).

Results

Baseline characteristics of patients with diabetes and without diabetes are provided in Table 1. In total, 215 patients (136, 63% men, mean age 58±11 years) were included of which 86 (40%) were patients with known type 2 diabetes mellitus. Ninety-six (45%) patients used statins (41 (48%) patients with diabetes, 55 (43%) without diabetes, p=0.47), 91 (42%) aspirin, 78 (36%) β-blockers and 69 (32%) angiotensin converting enzyme inhibitors. Patients with diabetes mellitus were significantly younger as compared to patients without diabetes, had a higher mean body mass index and lower prevalence of previous CAD.

Table 1. Characteristics of patients with diabetes and without diabetes

	All patients (n=215)	Patients with diabetes (n=86)	Patients without diabetes (n=129)
Age (yrs)*	58±11	56±11	59±12
Male gender	136 (63%)	56 (65%)	80 (62%)
Hypercholesterolemia	114 (53%)	53 (62%)	61 (47%)
Arterial hypertension	107 (50%)	48 (56%)	59 (46%)
Smoking	80 (37%)	33 (38%)	47 (36%)
Family history of CAD	82 (38%)	30 (35%)	52 (40%)
Body mass index (kg/m^2)*	27±4	28±5	26±4
Obesity	37 (17%)	20 (24%)	17 (14%)
Cardiac history			
Previous MI*	41 (19%)	8 (9%)	33 (26%)
Previous PCI*	42 (20%)	9 (11%)	33 (26%)

* p<0.05 between patients with and without diabetes.

Data are mean±SD or n (%).

CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

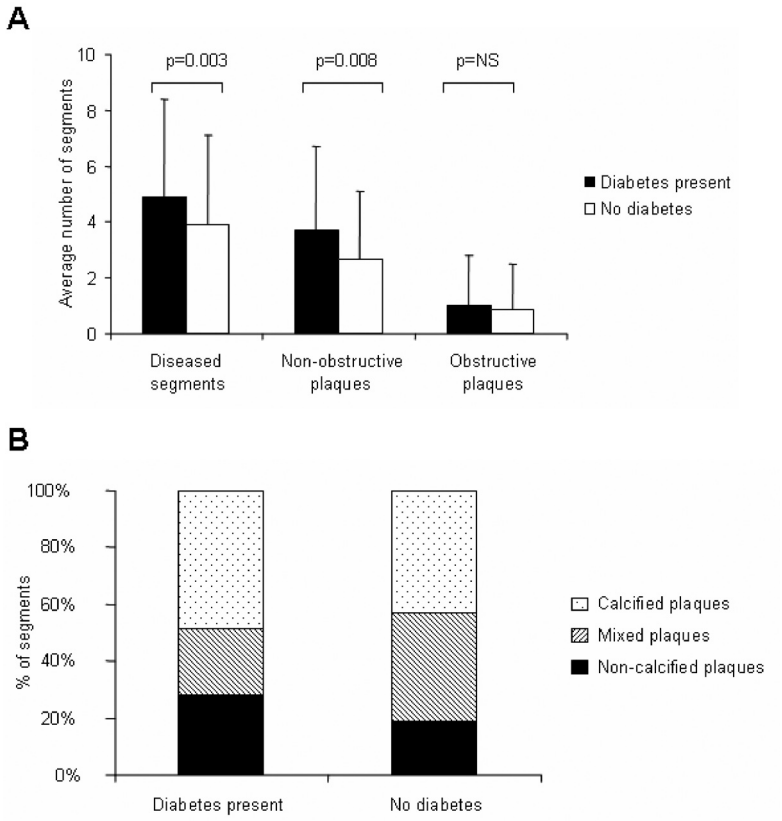

Figure 2. A. Clustered columns demonstrating the distribution of diseased coronary segments, segments with non-obstructive and obstructive plaques in diabetic and non-diabetic patients. B. Bar graph demonstrating the relative distribution of coronary segments with different plaque types in patients with diabetes mellitus and without diabetes ($p<0.0001$).

MSCT plaque characteristics

Total patient population

Coronary plaque characteristics on MSCT in the entire population and in patients presenting with or without diabetes mellitus are presented in Table 2 and Figure 2. After exclusion of 64 (2%) segments with non-diagnostic quality (n=11 small caliber, n=45 motion artefacts due to elevated heart rate, n=8 increased signal-to-noise ratio), a total of 2941 coronary segments were included in the analysis. CAD was completely absent on MSCT in 41 (19%) patients. In the remaining 174 (81%) patients 917 (31%) segments with plaques (n=871, 29%) or previously implanted stents (n=46, 2%) were observed. Of

segments containing plaques, 675 (77%) showed non-obstructive and 196 (23%) showed obstructive CAD. In general, non-calcified plaques were observed in 204 (23%) segments, mixed in 271 (31%) and calcified in 396 (46%).

Diabetic patients versus non-diabetic patients

As can be derived from Table 2, the average number of diseased segments was higher in patients with diabetes (4.9±3.5) as compared to non-diabetic patients (3.9±3.2), p=0.03. Particularly non-obstructive coronary plaques were more frequently observed on MSCT in the former population (Figure 2 A). In addition, CAD tended to be more severe in diabetic patients as both LM/LAD disease and multi-vessel disease were more frequently diagnosed, although the difference did not reach statistical significance.

Table 2. MSCT plaque characteristics in the whole study population and comparison between patients with diabetes and without diabetes

	All patients (n=215)	Patients with diabetes (n=86)	Patients without diabetes (n=129)
Patients			
Coronary plaques on MSCT	174 (81%)	73 (85%)	101 (78%)
Obstructive CAD	80 (37%)	34 (40%)	46 (36%)
Single vessel disease	43 (20%)	16 (19%)	27 (21%)
Multi-vessel disease	37 (17%)	18 (21%)	19 (15%)
Obstructive CAD in LM/LAD	61 (28%)	29 (34%)	32 (25%)
Total Agatston calcium score	73 (0-387)	72 (0-372)	74 (0-391)
Segments			
Nr of diseased segments*	4.3±3.4	4.9±3.5	3.9±3.2
Nr of segments with obstructive plaques	0.9±1.7	1.0±1.8	0.9±1.6
Nr of segments with non-obstructive plaques*	3.1±2.7	3.7±3.0	2.7±2.4
Nr of segments with non-calcified plaques*	1.0±1.6	1.3±2.0	0.7±1.2
Nr of segments with mixed plaques	1.3±1.8	1.1±1.5	1.4±2.0
Nr of segments with calcified plaques*	1.8±2.4	2.3±2.8	1.5±2.1

* $p<0.05$ between patients with and without diabetes.

Data are mean±SD, median (interquartile range) or n (%).

CAD, coronary artery disease; LAD, left anterior descending coronary artery; LM, left main coronary artery; MSCT, multi-slice computed tomography.

Concerning plaque types however, significant differences were observed in between diabetic and non-diabetic patients since patients with diabetes presented with significantly more segments containing non-calcified plaques (1.3±2.0 versus 0.7±1.2, p=0.005) as well as calcified plaques (2.3±2.8 versus 1.5±2.1, p=0.02). Accordingly, also the relative distribution

of plaque types, which is illustrated in Figure 2 B, differed since plaques in patients with diabetes were more frequently either non-calcified (114/406, 28% versus 90/465, 19%) or calcified (198/406, 49% versus 198/465, 43%). In contrast, plaques in patients with diabetes were less frequently mixed (94/406, 23% versus 177/465, 38%), p<0.0001.

Correlation of MSCT plaque characteristics and diabetes

The results of uni- and multivariate analyses of the correlation between MSCT plaque characteristics and the presence of diabetes are depicted in Table 3. After correction for baseline characteristics, the correlation of the number of diseased coronary segments as well as the number of segments with non-obstructive plaques and the presence of diabetes remained statistically significant. Concerning plaque type, both the number of coronary segments with non-calcified and calcified plaques remained significantly correlated with diabetes.

Table 3. Estimates of correlation of MSCT plaque characteristics with the presence of diabetes

	Univariate		Multivariate	
MSCT characteristics	Parameter estimate	p-value	Parameter estimate	p-value
Patients				
Total Agatston calcium score	127.91	0.11	139	0.08
Coronary plaques on MSCT	1.56 (0.76-3.21)	0.23	1.35 (0.56-3.26)	0.50
Non-obstructive CAD	1.53 (0.70-3.32)	0.28	1.11 (0.42-2.94)	0.83
Obstructive CAD	1.59 (0.72-3.52)	0.25	2.09 (0.68-6.49)	0.20
Obstructive CAD in LM/LAD	1.70 (0.77-3.74)	0.19	2.89 (0.90-9.31)	0.08
Single vessel disease	1.11 (0.46-2.67)	0.82	1.35 (0.43-4.29)	0.61
Multi-vessel disease	1.77 (0.72-4.35)	0.21	4.78 (0.66-34.37)	0.12
Segments				
Nr of diseased segments	1.01	0.03	1.51	0.0004
Nr of segments with obstructive plaques	0.13	0.58	0.33	0.17
Nr of segments with non-obstructive plaques	0.99	0.008	1.27	0.0005
Nr of segments with non-calcified plaques	0.63	0.006	0.69	0.004
Nr of segments with mixed plaques	-0.28	0.28	0.03	0.91
Nr of segments with calcified plaques	0.77	0.02	0.88	0.008

Data are odds ratios (CI) or estimates of correlation.

CAD, coronary artery disease; LAD, left anterior descending coronary artery;
LM, left main coronary artery; MSCT, multi-slice computed tomography.

Discussion

In the present study, differences in coronary plaque characteristics between patients with and without diabetes mellitus were observed using MSCT coronary angiography. A significant, positive correlation between the presence of diabetes and coronary plaque extent was demonstrated. In particular, diabetes was associated with an increased number of non-obstructive plaques, indicating more diffuse CAD as compared to patients without diabetes. Also, differences in the distribution of coronary plaque types were observed, with diabetic patients showing more non-calcified and calcified plaques and less mixed plaques.

Plaque burden

In the present study, a larger plaque burden was observed in patients with diabetes. Similar observations have been reported in previous invasive as well as postmortem studies.[22,23] Nicholls et al recently reported observations in 654 subjects (including 128 with diabetes) using intravascular ultrasound; the authors demonstrated that diabetes was a strong, independent predictor of percent plaque volume and total atheroma volume, indicating that diabetes appears to be associated with a substantial increase in (diffuse) plaque burden.[23]

In addition, diabetes was associated with more non-obstructive plaques in current study. This has also been observed in studies using invasive coronary angiography.[8,9] The increased total plaque burden may be related with the increased event rate, as observed in diabetic patients. Moreover, it has been suggested that plaque rupture may occur often in non-obstructive lesions, referred to as vulnerable plaques.[24-27] Many of these non-obstructive lesions will not be associated with stress-inducible ischemia, resulting in normal results on functional imaging tests, such as nuclear imaging or stress echocardiography.[28,29] Whether the larger total plaque burden and the increased prevalence of non-obstructive lesions in diabetic patients translate into a higher event rate remains to be determined in future studies.

Plaque composition

Another important finding of the present study is the difference in distribution of different coronary plaque types between patients with and without diabetes. Relatively more non-calcified and calcified plaques were observed in patients with diabetes. At the same time, the proportion of mixed plaques (possibly regarded as an intermediate phase of coronary plaque development) was significantly lower in patients with diabetes. Accordingly, these observations could suggest a more rapid development of atherosclerosis in the presence of diabetes, with faster progression from non-calcified lesions to completely calcified lesions. A faster progression of atherosclerosis in patients with diabetes has been suggested

previously based on event rates in patients undergoing nuclear perfusion imaging.[6,30] In the general population, a normal perfusion scan is associated with a low (<1%) hard event rate which is sustained over long-term follow-up. In patients with diabetes, the hard event rate is equally low in the first 2 years in patients with a normal perfusion scan, but an increased event rate (despite the initial normal myocardial perfusion scan) is observed after 2 years follow-up. This observation has been considered to be related to a faster progression of CAD in diabetic patients.

The increased prevalence of both non-calcified and calcified plaques may also have implications for calcium scoring. In a recent study by Raggi et al, 10,377 asymptomatic individuals (including 903 patients with diabetes) were followed for a period of 5±3.5 years after coronary calcium scoring with electron beam computed tomography.[31] Higher mortality was observed in diabetic patients as compared to non-diabetic patients despite similar coronary calcium scores, a finding which was observed for every level of coronary calcification. The authors hypothesized that the difference in prognosis in diabetic and non-diabetic patients despite similar calcium load could be attributed to the presence of extensive diffuse non-calcified atherosclerosis, which could not be detected by calcium scoring. In line with these suggestions, the current study indeed demonstrated the presence of diffuse atherosclerosis with a significantly higher amount of non-calcified coronary plaques in the diabetic patients. Accordingly, calcium scores may underestimate total coronary plaque burden to higher extent in patients with diabetes, and thus, MSCT coronary angiography may have substantial incremental value over coronary calcium scoring, although this concept needs further study.

Limitations

This study is a comparative study, describing coronary atherosclerosis in patients with and without diabetes. Examinations were performed at a single time point and were not repeated over time. Also, MSCT angiograms were evaluated visually since no reliable quantitative algorithms are currently available. Two scanner generations (16- and 64-slice MSCT) were used during the study, which could have affected the accuracy of detection of different plaque types. Follow-up data are not yet available and these data are needed to determine whether the observations on MSCT may provide prognostic information and may potentially be used to identify diabetic patients at increased risk. Finally, patients in the present study were referred for non-invasive cardiac evaluation of chest pain with known or suspected CAD. Accordingly, the findings may not be applicable to asymptomatic diabetic patients.

In addition, several limitations of MSCT in general should be mentioned. MSCT is still associated with an elevated radiation dose, while also the administration of contrast media is required. Finally, the presence of ischemia cannot be determined on MSCT and abnormal MSCT findings should ideally be combined with functional data.

Conclusions

Differences in coronary plaque characteristics on MSCT were observed between patients with diabetes and without diabetes. Diabetes may be associated with a higher coronary plaque burden as determined on MSCT. Also, more non-calcified and calcified plaques in combination with less mixed plaques were observed in patients with diabetes, possibly reflecting faster progression of CAD in the presence of diabetes. MSCT may be used to identify differences in coronary plaque burden, which may eventually be useful for risk stratification of patients with diabetes.

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Chapter 11

Type 2 Diabetes is Associated With More Advanced Coronary Atherosclerosis on Multislice Computed Tomography and Virtual Histology Intravascular Ultrasound

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Abstract

Background: Data on coronary plaque observations on multi-slice computed tomography (MSCT) in patients with type 2 diabetes are scarce.

Methods: In tota, 60 patients (19 with diabetes) underwent 64-slice MSCT, followed by conventional coronary angiography with intravascular ultrasound (IVUS). Non-invasively, the extent of coronary atherosclerosis and 3 plaque types (non-calcified, calcified, mixed) were visually evaluated on MSCT. Invasively, plaque burden was assessed on gray-scale IVUS. Plaque composition was evaluated on virtual histology intravascular ultrasound (VH IVUS).

Results: Concerning geometrical plaque data, diabetic patients showed more plaques on MSCT (7.1±3.2 versus 4.9±3.2 in non-diabetic patients, p=0.01). On gray-scale IVUS, diabetes was associated with a larger plaque burden (48.7±10.7% versus 40.0±12.1%, p=0.003). Concerning plaque composition, diabetes was associated with more calcified plaques on MSCT (52% versus 24%). Relatively more fibrocalcific plaques in diabetic patients (29% versus 9%) were observed on VH IVUS. Moreover, these plaques contained more necrotic core (10.8±5.9% versus 8.6±5.2%, p=0.01).

Conclusions: A higher plaque extent and more calcified lesions were observed in diabetic patients on MSCT. The findings were confirmed on gray-scale and VH IVUS. Thus, MSCT may potentially be used to explore patterns of coronary atherosclerosis in diabetic patients.

Introduction

Type 2 diabetes is strongly associated with the development of coronary artery disease (CAD).[1] Thus far, functional testing has been used to detect CAD in diabetic patients, including myocardial perfusion scintigraphy and stress echocardiography. Although abnormal test results have been clearly associated with the development of cardiovascular events on follow-up, elevated event rates have also been observed in patients without detectable ischemia.[2,3] These findings suggest that to some extent the increased cardiovascular risk in patients with diabetes could be attributed to the presence of diffuse CAD rather than focal high-grade lesions.

Accordingly, direct visualization of coronary atherosclerosis could be superior to detection of ischemia for risk stratification of diabetic patients. Both non-invasive and invasive modalities are currently available and may be useful for this purpose. The available studies thus far have mainly addressed the quantification of plaque burden. Indeed, diabetes was demonstrated to be a strong predictor of increased atherosclerotic volume on gray-scale intravascular ultrasound (IVUS).[4] Non-invasively, increased calcific plaque burden was observed in diabetic patients on electron beam computed tomography.[5] Nonetheless, although the above techniques allow estimation of coronary plaque extent, they are suboptimal for the assessment of plaque composition.

Recently, multi-slice computed tomography (MSCT) coronary angiography was introduced, which in addition to visualization of obstructive and non-obstructive plaques allows assessment of plaque composition.[6,7] Invasively, plaque composition may be evaluated by virtual histology IVUS (VH IVUS).[8] However, only limited data are available on plaque characterization by both techniques in diabetic patients. Accordingly, the purpose of the study was to evaluate coronary plaque extent and composition on MSCT and to compare these findings with patterns of coronary atherosclerosis on invasive angiography, gray-scale IVUS and VH IVUS. Patients with and without diabetes were compared.

Methods

Patients and study protocol

A total of 60 patients, 19 (32%) patients with type 2 diabetes and 41 (68%) patients without diabetes, were included in the study. All patients presented with chest pain suggestive of CAD. Diabetes was diagnosed according to the criteria as set by the American Diabetes Association:[9] 1) a fasting plasma glucose level of ≥7.0 mmol/l or 2) symptoms of diabetes and a casual plasma glucose level of ≥11.1 mmol/l. The patients

with a long history of diabetes and requiring insulin and oral hypoglycemic agents were also diagnosed as having diabetes. Patients underwent 64-slice MSCT coronary angiography, followed within a month by conventional coronary angiography in combination with IVUS of 1 to 3 vessels. The clinical history of the patients was evaluated prior to conventional coronary angiography to ensure that neither acute coronary events nor worsening of angina occurred between the examinations.

Patients were excluded from the study if contraindications for MSCT were present.[10] IVUS examination was not performed if severe vessel tortuousness, severe luminal narrowing precluding the insertion of the IVUS catheter or vessel occlusion were present. Informed consent was obtained from all patients.

MSCT

Image acquisition

MSCT coronary angiography was performed using a 64-detector row Toshiba Aquilion (Toshiba Medical Systems, Tokyo, Japan) scanner. A helical scan protocol with electrocardiographic gating was applied as described previously.[11] Additional oral β-blockers (metoprolol, 50 or 100 mg, single dose, 1 hour prior to the examination) were provided if the heart rate was ≥60 beats/min and no contraindications for the use of β-blockers were present. The image dataset was initially reconstructed at the diastolic phase of the R-R interval (75% of the R-R interval). In case of the presence of motion artefacts additional phases were explored. The middle segment of the right coronary artery was verified in the end-systolic image reconstruction dataset in all patients with good image quality at end-diastolic phase. Image reconstructions obtained with either smooth or medium filters were used for the evaluation of non-calcified plaques in all patients. In the presence of extensive calcifications, reconstructions obtained with a sharp filter were additionally analyzed to verify calcium containing plaques.

Image analysis

Images were evaluated on a remote workstation with dedicated software (Vitrea 2, Vital Images, Minnetonka, Minnesota, USA and Advantage, GE Healthcare, Boston, Massachusetts, USA). Two experienced observers evaluated the examinations side-by-side in consensus. The presence, extent and type of coronary plaques was assessed using a qualitative visual approach as previously described.[12] Briefly, the plaques were assessed using axial images and curved multiplanar reconstructions. Plaques were defined a structures >1 mm^2 within and/or adjacent to the coronary artery lumen, which

could be clearly distinguished from the vessel lumen and the surrounding tissue. Plaques were visually classified as obstructive or not, using a threshold of 50% luminal narrowing. Three types of plaques were distinguished: non-calcified (composed only of low-density component), mixed (composed of both low- and high-density components) and calcified (composed only of high-density component).

Conventional coronary angiography and quantitative coronary angiography analysis

Conventional invasive coronary angiography was performed according to standard protocols. An experienced observer performed off-line quantitative coronary angiography (QCA) analyses, using dedicated software (QCA CMS 6.0, Medis Medical imaging systems, Leiden, The Netherlands). For each vessel examined both with MSCT and IVUS, percent luminal narrowing was reported at the site of the minimal lumen area (MLA).

Gray-scale and VH IVUS
Image acquisition

IVUS examinations were performed with a 20 MHz, 2.9 F phased-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, California, USA). After intracoronary administration of nitrates, the catheter was introduced to the distal coronary artery and withdrawn at a continuous speed of 0.5 mm/s to the coronary ostium using automated pullback device (Track Back, Volcano Corporation, Rancho Cordova, California, USA). To define the starting position of the IVUS catheter, cine runs before and during contrast injection were performed. The images were stored for off-line analysis.

Image analysis

Gray-scale IVUS. To evaluate geometrical plaque parameters, gray-scale IVUS datasets were evaluated on a vessel level by an experienced observer, using dedicated software (QCU CMS 4.0 Medis Medical imaging systems, Leiden, The Netherlands). Cross-sectional images spaced 0.5 mm apart in the pullback were analysed within the full length of the examined vessel. First, the contours of the external elastic membrane (EEM) were identified and the mean EEM area was calculated in the examined vessel. Subsequently, lumen-intima interface was identified and mean lumen area was calculated. Plaque area was enclosed by the contours of the EEM and the lumen-intima interface and mean plaque area was identified per vessel. Plaque burden was calculated as the percentage of the EEM occupied by plaque [Plaque burden (%)=$\Sigma(EEM_{area}\text{-}lumen_{area})/\Sigma\ EEM_{area}$ x 100].

Percent of abnormal images (having a maximal plaque thickness >0.5 mm) was calculated in each examined vessel.[13] Finally, remodeling index was calculated by dividing the EEM area at MLA site of the vessel by the EEM area at proximal reference site. The latter was defined as the frame with largest lumen area located within 10 mm from the MLA frame with no major intervening side branches.[14]

Of note, the accuracy of the IVUS pullback device was assessed by imaging single stents of known length (8 to 18 mm stents) in a subpopulation of 15 patients (5 stents in the right coronary artery, 5 stents in the left anterior descending coronary artery, 5 stents in the left circumflex coronary artery). In all included patients, the pullback was available at least 10 mm beyond the distal end of the stent and at least 10 mm proximal to the stent. The stents were measured between the distal and proximal IVUS frames with complete circumferential appearances of the stent struts.

VH IVUS. An experienced observer performed quantitative VH IVUS image analysis on a plaque level using dedicated software (pcVH 2.1, Volcano Corporation, Rancho Cordova, California, USA). Qualitative VH IVUS analysis was performed in consensus by 2 experienced observers. First, 4 tissues were differentiated and labelled with different colours (fibrotic, fibro-fatty tissues, necrotic core and dense calcium), as described and validated previously.[8,15] The mean percentage of each plaque component was obtained in the full length of each plaque observed on MSCT. In addition, plaques were visually assessed in 3 consecutive frames within 10 mm from the MLA site of plaque and were classified into 4 different types based on geometrical and compositional parameters as well as the location of specific components in the plaque: (1) Pathological intimal thickening, 2) Fibroatheroma, 3) Thin cap fibroatheroma, and 4) Fibrocalcific plaque.[16,17]

Plaques were matched between MSCT and VH IVUS as previously described.[18] First, plaques were visually identified on MSCT. The distances from the established landmarks (coronary ostia, side-branches) to the starting point and the termination point of the plaques were measured on multiplanar reconstructions of the vessels on MSCT. These distances were subsequently measured on the longitudinal mode of IVUS datasets. The transversal IVUS sections were further inspected and the starting and the termination frames of the lesions were depicted.

Statistical analysis

Categorical variables are expressed as numbers (percentages) and compared between groups with 2-tailed Chi-square test. When normally distributed, continuous variables are expressed as means (standard deviation) and compared with the 2-tailed t-test for independent samples. When not normally distributed, continuous variables are expressed

as medians (interquartile range) and compared with the 2-tailed non-parametric Mann-Whitney test. To evaluate the reproducibility of coronary plaque evaluation on MSCT and VH IVUS Cohen's kappa coefficient was calculated. The agreement of QCA analysis was expressed as the difference of percent diameter stenosis between the measurements.

P-values <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS software (version 14.0, SPSS Inc, Chicago, Ill, USA).

Results

Baseline clinical characteristics of patients with diabetes and without diabetes are provided in Table 1.

Table 1. Characteristics of patients with diabetes and without diabetes

	Patients with diabetes (n=19)	Patients without diabetes (n=41)	p value
Age (y)	60±10	58±11	0.4
Male gender	14 (74%)	21 (51%)	0.1
BMI (kg/m^2)	27.4±3.6	26.3±3.7	0.3
HbA1c (%)	7.1±1.4	-	-
Risk factors			
Hypercholesterolemia	18 (95%)	31 (76%)	0.08
Arterial hypertension	12 (63%)	24 (59%)	0.7
Smoking	9 (47%)	20 (49%)	0.9
Family history of CAD	5 (26%)	23 (56%)	0.03
Obesity	5 (26%)	8 (20%)	0.6
History of CAD			
Previous MI/PCI	9 (47%)	12 (29%)	0.2
Medication			
ACEI or ARB	12 (63%)	20 (49%)	0.3
Beta-blockers	9 (47%)	23 (56%)	0.5
Aspirin	14 (74%)	28 (68%)	0.7
Statins	18 (95%)	26 (63%)	0.01
Oral hypoglycemic agents	19 (100%)	-	-
Insulin	5 (26%)	-	-

Data are mean±SD or n (%).

ACEI, angiotenzin converting enzyme inhibitors; ARB, angiotenzin receptor blockers; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Geometrical data of coronary atherosclerosis (plaque extent)

MSCT. MSCT coronary angiograms were of diagnostic quality in all patients. A good intra- and inter-observer agreement was observed for the detection of obstructive plaques (Cohen's kappa coefficient 0.81 for intra-observer variability and 0.81 for inter-observer variability). The results of the geometrical analysis on MSCT are presented in Table 2. The average number of coronary plaques was higher in diabetic patients as compared with patients without diabetes. In particular, a trend for a higher number of non-obstructive plaques was observed in diabetic patients (5.2±2.7 in patients with diabetes versus 3.8±2.6 in patients without diabetes, p=0.06).

Table 2. Geometrical data of coronary atherosclerosis on MSCT, gray-scale IVUS and QCA in patients with diabetes and without diabetes

	Diabetes present (n=19 patients)	No diabetes (n=41 patients)	p value
MSCT	n=57 vessels (134 plaques)	n=123 vessels (201 plaques)	
Total Agatston calcium score	282 (54-578)	85 (3-326)	0.09
CAD present	19 (100%)	41 (100%)	1.0
Obstructive CAD	13 (68%)	22 (54%)	0.3
Non-obstructive CAD	6 (32%)	19 (46%)	0.3
Nr of vessels with any plaques	2.6±0.7	2.2±0.8	0.08
Nr of vessels with obstructive plaques	1.3±1.2	0.9±1.1	0.2
Nr of vessels with non-obstructive plaques	2.5±0.8	2.0±1.0	0.08
Nr of any plaques	7.1±3.2	4.9±3.2	0.02
Nr of obstructive plaques	1.9±2.1	1.2±1.7	0.2
Nr of non-obstructive plaques	5.2±2.7	3.8±2.6	0.06
Gray-scale IVUS and QCA	n=36 vessels	n=81 vessels	
Examined vessel length (cm)	10.3±8.7	8.3±9.3	0.4
Mean EEM area (mm^2)	15.1±4.6	14.1±5.2	0.4
Mean lumen area (mm^2)	7.8±2.8	8.2±2.8	0.5
Mean plaque area (mm^2)	7.4±3.1	5.9±3.5	0.07
Plaque burden (%)	48.7±10.7	40.0±12.1	0.003
Percent abnormal frames in the full length of the vessel (%)	90.4±14.8	77.4±27.1	0.03
Lesion luminal narrowing on QCA (%)	33.8±13.4	28.5±17.5	0.3
Remodeling index at the site of MLA	0.95±0.07	0.97±0.12	0.4

Data are mean±SD, median (interquartile range) or n (%).

CAD, coronary artery disease; EEM, external elastic membrane; IVUS, intravascular ultrasound; MLA, minimal lumen area; MSCT, multi-slice computed tomography; QCA, quantitative coronary angiography.

QCA and gray-scale IVUS. A good intra- and inter-observer agreement was observed for the evaluation of stenosis severity on QCA (mean difference 7.4±7.2% and 8.1±7.4%, respectively). Similarly, a good accuracy of the IVUS pullback device was observed. The difference in known and measured stent length was 1.7±0.8 mm (p=0.4), whereas the deviation from known stent length was 10.9±3.5%. Geometrical coronary plaque data obtained by QCA and gray-scale IVUS are presented in Table 2. Briefly, on gray-scale IVUS, more diffuse atherosclerosis was observed in diabetic patients as reflected by a larger plaque burden in the presence of diabetes. In addition, the number of abnormal IVUS frames was also higher in patients with diabetes. An example of diffuse atherosclerosis in a patient with type 2 diabetes on MSCT and gray-scale IVUS is provided in Figure 1.

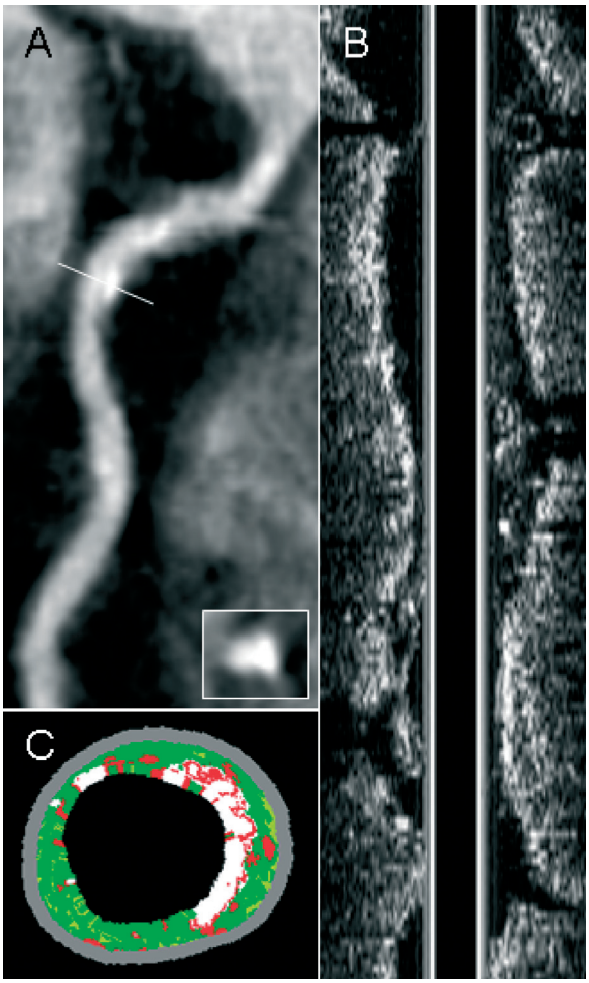

Figure 1. An example of coronary atherosclerosis in a patient with type 2 diabetes as demonstrated by MSCT (A), gray-scale IVUS (B) and VH IVUS (C). (A) MSCT multiplanar reconstruction of the right coronary artery, demonstrating diffuse atherosclerosis along the course of the artery. A mixed plaque is observed in the proximal part of the vessel both on longitudinal and the transversal images. (B) The presence of diffuse atherosclerosis was confirmed on the longitudinally reconstructed gray-scale IVUS image. (C) The corresponding image on VH IVUS at the site of MLA of the plaque, depicting a lesion with the features of fibrocalcific plaque.
IVUS, intravascular ultrasound; MSCT, multi-slice computed tomography; MLA, minimal lumen area; VH IVUS, virtual histology intravascular ultrasound.

Compositional data of coronary atherosclerosis

MSCT. A good agreement was observed for the classification of plaque type (Cohen's kappa coefficient 0.85 for intra-observer variability and 0.74 for inter-observer variability). As shown in Table 3, relatively more calcified plaques were observed in diabetic patients as compared with patients without diabetes. The proportion of mixed plaques was similar between the 2 patient populations, whereas non-calcified plaques were relatively more prevalent in patients without diabetes.

Table 3. Compositional data of coronary plaques on MSCT and VH IVUS in patients with diabetes and without diabetes

	Diabetes present	No diabetes	p value
MSCT	n=134 plaques	n=201 plaques	
Nr of calcified plaques	70 (52%)	49 (24%)	<0.001
Nr of mixed plaques	41 (31%)	82 (41%)	0.06
Nr of non-calcified plaques	23 (17%)	70 (35%)	<0.001
VH IVUS	n=59 plaques	n=110 plaques	
Average percentage of plaque components			
Fibrotic (%)	56.0±7.6	57.7±8.8	0.2
Fibro-fatty (%)	26.8±9.9	29.1±11.8	0.2
Necrotic core (%)	10.8±5.9	8.6±5.2	0.01
Dense calcium (%)	6.4±6.3	4.5±4.3	0.02
Plaque types			
Fibrocalcific plaque	17 (29%)	10 (9%)	0.001
Fibroatheroma	28 (47%)	52 (47%)	0.98
Thin cap fibroatheroma	4 (7%)	11 (10%)	0.4
Pathological intimal thickening	10 (17%)	37 (34%)	0.02

Data are mean±SD or n (%).

MSCT, Multi-slice computed tomography; VH IVUS, virtual histology intravascular ultrasound.

VHIVUS. The results of coronary plaque composition on VH IVUS are presented in Table 3. Briefly, the amount of dense calcium was larger in the plaques of patients with diabetes as compared with patients without diabetes. Moreover, the plaques of diabetic subjects contained more necrotic core. A good agreement was observed for the classification of plaque type (Cohen's kappa coefficient 0.75 for intra-observer variability and 0.87 for inter-observer variability). Qualitative assessment of lesions revealed a higher prevalence of fibrocalcific plaques in diabetic patients. In contrast, in patients without diabetes relatively more lesions were classified as pathological intimal thickening. No differences, however, were observed in the prevalence of fibroatheroma and thin cap fibroatheroma. An example of a mixed plaque on MSCT and the corresponding plaque demonstrating features of fibrocalcific plaque on VH IVUS is provided in Figure 1.

Discussion

The findings of coronary plaque characterization using MSCT angiography, gray-scale and VH IVUS may be summarized as follows. First, the extent of coronary plaques was higher in diabetic patients on MSCT. This finding corresponded with more diffuse atherosclerosis and a larger plaque burden on gray-scale IVUS examination. Second, the proportion of completely calcified plaques on MSCT was larger in patients with diabetes as compared with patients without diabetes. On VH IVUS, this corresponded with a larger amount of dense calcium and a higher prevalence of fibrocalcific plaques. Finally, a larger amount of necrotic core was observed in the plaques of diabetic patients, whereas the prevalence of TCFA was identical between the 2 patient populations.

Plaque extent

In the present study, a higher extent of coronary atherosclerosis was observed in diabetic patients both on MSCT and on gray-scale IVUS. A trend towards a higher number of non-obstructive plaques was observed although the finding was not statistically significant. This finding is in line with a previous study exploring non-invasive coronary plaque characterization on MSCT angiography.[12] Indeed, in this study including 215 patients (86 patients with type 2 diabetes) diabetes was associated with a higher prevalence of non-obstructive coronary plaques.[12] Moreover, the observation on MSCT in the present study was paralleled by a more diffuse atherosclerosis and a larger plaque burden on gray-scale IVUS. Similar observations were reported by Nicholls et al [4] who reported on the measures of coronary plaques on gray-scale IVUS in 654 patients, of which 128 with diabetes. The authors reported a significantly larger plaque burden in diabetic patients. Increased plaque extent on MSCT as well as on gray-scale IVUS (namely due to non-obstructive and thus predominantly non-flow limiting plaques) might explain a higher event rate in diabetic population. Indeed, it has been observed that plaques leading to myocardial infarction are most often non-obstructive on invasive angiography months prior to the occurrence of the event.[19] Moreover, pathological studies of the victims of sudden cardiac death have shown that the cross sectional area luminal narrowing was below 75% (luminal narrowing of less than 50%) in more than 80% of plaques referred to as vulnerable to rupture.[20] Nevertheless, it remains to be determined in follow-up studies whether a higher plaque extent as observed on MSCT may be able to predict the increased cardiovascular event rate in diabetic patients.

A trend for a larger EEM area was observed in the diabetic patients of the present study population. Moreover, in accordance to the observations by Nicholls et al,[4] the degree of stenosis on QCA and the remodeling index of the lesions of the present study did not differ between

the 2 patient populations, although more plaque was observed in diabetic patients. The discrepancy could be explained by the presence of diffuse atherosclerosis also in the reference segment of plaques of diabetic patients, as previously reported.[21] As a consequence, the QCA measurements as well as the remodeling index may underestimate the actual plaque burden. Moreover, previous studies showed that coronary arteries of diabetic patients tend to undergo negative remodeling.[21,22] Nevertheless, no correlation between vessel shrinkage and the presence of diabetes was observed in the present study. Indeed, contrary to previous studies the majority of coronary arteries that were examined invasively in the present study contained non-obstructive plaques. In addition, only a small proportion of patients in the current study were insulin dependent, whereas negative remodeling may be more strongly related to insulin treatment than to non-insulin dependent diabetes.[22]

Plaque composition

In the present study, the proportion of completely calcified plaques on MSCT was larger in patients with diabetes as compared with patients without diabetes. Similar observations on coronary calcifications were reported in previous studies using electron beam computed tomography and MSCT.[5,12] Indeed, in a recent MSCT study 49% of plaques were classified as completely calcified in diabetic patients.[12] In contrast to the above study, however, diabetic patients in the present study contained a larger proportion of mixed plaques and a smaller proportion of non-calcified plaques. This finding could be explained by a higher risk profile of patients as compared to the population of the previous study. Accordingly, atherosclerosis could be more advanced (with more extensive calcifications) in these patients. As a consequence, the number of mixed plaques was identical in diabetic patients and patients without diabetes.

In accordance with the findings on MSCT, a larger amount of dense calcium was observed in the plaques of diabetic patients on VH IVUS. This observation is in line with a pathological study by Burke et al [23] who demonstrated that type 2 diabetes was associated with a larger area of calcified matrix. Similar findings were recently reported by Nasu et al [24] who investigated coronary plaque composition on VH IVUS in the target vessels of 36 type 2 diabetic patients and compared the findings with patients without diabetes; the authors reported a larger amount of dense calcium in the lesions of diabetic patients. On visual evaluation, more plaques of diabetic patients in the present study contained features of fibrocalcific plaque. Indeed, based on pathological investigations fibrocalcific plaque may resemble the healing process following previous plaque ruptures or erosions and accordingly represent advanced atherosclerotic lesions.[17]

Finally and importantly, together with the presence of extensive calcifications a larger amount of necrotic core was observed in the plaques of diabetic patients on VH IVUS. Indeed, increased amount of necrotic core was shown to be a feature of increased risk to plaque rupture.[20] Nevertheless, the proportion of TCFA (the precursor lesion of plaque rupture) was identical in diabetic patients and in patients without diabetes. The explanation of these findings may be twofold. First, the patients of the study were extensively treated with cardiovascular medication, which possibly could have resulted in a more stabilized coronary plaque profile and thus decreased development of TCFA. Second, the coexistence of more extensive calcifications and the absence of direct evidence of vulnerable plaque morphology on VH IVUS may imply different pathophysiological mechanisms of plaque instability in diabetes.[23] Further studies are necessary to better understand the mechanisms that lead to plaque instability and cardiovascular events in diabetic patients.

Limitations

The findings of the study are based on a relatively small patient population. Concerning MSCT, the technique is still associated with an elevated X-ray dose, while also the administration of contrast material is required. Also, no validated algorithms that allow quantification of plaque stenosis, volume and composition are available for MSCT at present. Thus, in the present study MSCT studies were analyzed using a qualitative visual approach, without the use of dedicated software algorithms or attenuation value measurements. The limitation of VH IVUS is the fact that the technique is relatively new, expensive and not widely available. As a result, the current observations need confirmation in future studies. In addition, both gray-scale IVUS and VH IVUS are invasive techniques and accordingly associated with risk. As a result their use remains restricted to symptomatic patients. Importantly, these investigations in larger patient cohorts should also include follow-up, as data on the potential prognostic value of both MSCT and VH IVUS are limited. Further studies should address whether certain plaque characteristics in diabetic patients may indeed be related to adverse outcome.

Conclusions

In conclusion, differences in coronary plaque patterns were observed on MSCT, gray-scale and VH IVUS between patients with versus without diabetes. Diabetes was associated with a higher plaque extent as determined both on MSCT and gray-scale IVUS. Concerning plaque composition, more calcified plaques were observed on MSCT in patients with diabetes. On VH IVUS, plaques of diabetic patients contained a larger amount of dense calcium and were of a more advanced stage based on visual qualification. Thus, MSCT may potentially be used to explore patterns of coronary atherosclerosis in diabetic patients.

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Chapter 12

Gender-Specific Differences in Extent and Composition of Coronary Atherosclerotic Plaques in Relation to Age: Non-invasive Assessment With Multi-Slice Computed Tomography and Invasive Evaluation With Gray-Scale and Virtual Histology Intravascular Ultrasound

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Submitted

Abstract

Aims: We evaluated coronary plaque patterns in men and women in relation to age using multi-slice computed tomography (MSCT). The findings were compared with observations on gray-scale and Virtual Histology (VH) intravascular ultrasound (IVUS).

Methods: 93 patients (59 men, 34 women) underwent 64-slice MSCT followed by conventional coronary angiography with IVUS. Plaque extent and composition were assessed on MSCT, gray-scale and VH IVUS. Coronary plaque patterns were compared between men and women in 2 age groups (<65 and ≥65 years old).

Results: More plaques were observed on MSCT in younger men (6±4 versus 2±2 in women, $p<0.001$). A larger plaque burden was observed on gray-scale IVUS (45.7±11.4% versus 36.3±11.6%, $p<0.001$). Similarly, more mixed plaques were observed in younger men (3±3 versus 1±1, $p=0.003$), whereas a larger arc of calcium was detected on gray-scale IVUS (91.7±93.5 versus 25.7±51.0 degrees, $p<0.001$). On VH IVUS, the prevalence of thin cap fibroatheroma was higher in younger men (31% versus 0%). No differences in plaque patterns were observed in older patients.

Conclusions: More extensive atherosclerosis and more calcified lesions were observed in men as compared with women. Moreover, these differences were predominantly present in younger patients and were lost in older patients.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality not only for men but also for women. Moreover, although cardiovascular mortality has declined in the male population over the years, no substantial decrease has been observed in women.[1-3]

Accordingly, timely assessment of CAD in women is currently being increasingly recognized as a clinically relevant issue. Nevertheless, the diagnosis of CAD appears to be more complicated in women. First, gender differences in clinical presentation of CAD have been observed.[4] The initial presentation of CAD in women is frequently rather atypical, whereas men relatively more often present with more typical symptoms of CAD. Second, the traditional diagnostic evaluation strategies have been validated in men and may be less suited for women.[4] Indeed, recent investigations have increased our awareness that gender-specific differences may exist in the pathophysiology of CAD.[5] In general, premenopausal women tend to have lower prevalences of obstructive CAD as compared with age-matched men. In fact, a ~10 year lag in the development of clinically overt CAD has been reported in women, although this difference tends to diminish in the seventh decade.[6] However, despite the absence of evident obstructive culprit lesions in women, their prognosis may not be considered benign with regard to symptoms and future events.[7-10]

Accordingly, direct visualization of coronary atherosclerosis rather than testing for obstructive CAD may be more appropriate for the initial assessment of CAD in women. While plaque burden is traditionally evaluated invasively using intravascular ultrasound (IVUS),[11,12] also non-invasive imaging methods have become available for this purpose. In previous studies, coronary calcium scoring has been used to evaluate age and gender differences in the extent of coronary calcium.[13,14] More detailed information, including stenosis severity and plaque composition, can be derived using Multi-Slice Computed Tomography (MSCT).[15-17] Possibly, MSCT coronary angiography may become a useful technique for the initial evaluation of CAD in women. However, data evaluating gender-specific differences in plaque observations on MSCT are scarce, but highly needed to understand the potential value of MSCT in this population. In addition, as the extent of these gender-specific differences may be highly influenced by age, it is important to establish whether these observations hold true for both younger and older patients.

Thus, the purpose of the study was to evaluate gender-specific differences in coronary plaque extent and composition in relation to age using non-invasive MSCT. Coronary plaque patterns were compared between men and women with further division into younger (<65 years old) and older (≥65 years old) patients. The findings were compared with invasive coronary plaque observations obtained with gray-scale and Virtual Histology (VH) IVUS.

Methods

Patient population and study protocol

A total of 93 patients were included in the study. All patients presented with chest pain suggestive of CAD. Patients underwent 64-slice MSCT coronary angiography, followed within a month by conventional coronary angiography in combination with gray-scale and VH IVUS of 1 to 3 vessels. The clinical history of the patients was evaluated prior to conventional coronary angiography to ensure that neither acute coronary events nor worsening of angina occurred between the examinations.

Patients were excluded from the study if contraindications for MSCT were present.[18] IVUS examination was not performed if severe vessel tortuousness, severe luminal narrowing precluding the insertion of the IVUS catheter or vessel occlusion were present. Informed consent was obtained from all patients.

For comparisons, the patient population was first divided based on gender (men versus women) and secondly based on age (younger (<65 years old) patients versus older (≥65 years old) patients).

MSCT

Image acquisition

MSCT coronary angiography was performed using a 64-slice Toshiba Aquilion (Toshiba Medical Systems, Tokyo, Japan) scanner. A helical scan protocol with electrocardiographic gating was applied as described previously.[19]

Image analysis

Images were evaluated on a remote workstation with dedicated software (Vitrea 2, Vital Images, Minnetonka, Minnesota, USA and Advantage, GE Healthcare, Boston, Massachusetts, USA). First, coronary Agatston calcium score was obtained from image dataset without contrast enhancement. Subsequently, 2 experienced observers evaluated the non-invasive coronary angiograms side-by-side in consensus. The presence of coronary plaques was visually assessed while scrolling through axial images and inspecting curved multiplanar reconstructions.[20] First, plaques were visually classified as obstructive or not using a threshold of 50% luminal narrowing. Second, the plaques were classified into 3 types: non-calcified (plaques having lower density as compared with the contrast-enhanced vessel lumen), mixed (plaques with non-calcified and calcified elements within the same plaque) and calcified (plaques having predominantly high density). The images were evaluated on a patient level. The mean number of any, non-obstructive and obstructive plaques was determined per patient. Likewise, the mean number of non-calcified, mixed and calcified plaques was determined per patient.

Gray-scale and VH IVUS

Image acquisition

IVUS examinations were performed with a 20 MHz, 2.9 F phased-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, California, USA). After intracoronary administration of nitrates, the catheter was introduced to the distal coronary artery and withdrawn at a continuous speed of 0.5 mm/s to the coronary ostium using automated pullback device. To define the starting position of the IVUS catheter, cine runs before and during contrast injection were performed. The images were stored for off-line analysis.

Image analysis, gray-scale IVUS

To evaluate geometrical plaque characteristics, gray-scale IVUS datasets were evaluated by an experienced observer, using dedicated software (QCU CMS 4.0 Medis Medical imaging systems, Leiden, The Netherlands). Cross-sectional images spaced 0.5 mm apart in the pullback were analyzed within the full length of the examined vessel. The contours of the external elastic membrane (EEM) were identified and the mean EEM area was calculated in the examined vessel. Subsequently, lumen-intima interface was identified and mean lumen area was calculated. Plaque area was enclosed by the contours of EEM and lumen. Plaque burden was calculated as the percentage of EEM occupied by plaque: [Plaque burden (%)=$\Sigma(EEM_{area}$-$lumen_{area})/\Sigma EEM_{area}$ x 100]. Plaque burden was identified per vessel. Plaque volume was determined in 10 mm of the vessel containing most and least plaque. Percent of abnormal images (having a maximal plaque thickness >0.5 mm) was calculated in each examined vessel.[21] Remodeling index was calculated by dividing the EEM area at the site with most plaque by the EEM area at proximal reference site. The latter was defined as the frame with largest lumen area located within 10 mm from the most diseased frame with no major intervening side branches.[22,23] Positive remodeling was considered as the remodeling index of ≥1.05. Finally, the largest arc of calcium in each examined vessel was obtained.

Image analysis, VH IVUS

An experienced observer performed quantitative VH IVUS image analysis on a plaque level using dedicated software (pcVH 2.1, Volcano Corporation, Rancho Cordova, California, USA). Qualitative VH IVUS analysis was performed side-by-side in consensus by 2 experienced observers. First, 4 tissues were differentiated and labeled with different colours (fibrotic, fibro-fatty tissues, necrotic core and dense calcium), as described and validated previously.[24,25] The mean percentage of each plaque component was obtained in

the full length of plaques observed on MSCT. In addition, plaques were visually assessed in 3 consecutive frames within 10 mm from the minimal lumen area site and were classified into 4 types based on geometrical and compositional parameters as well as the location of specific components in the plaque: (1) Pathological intimal thickening, 2) Fibroatheroma, 3) Thin cap fibroatheroma, and 4) Fibrocalcific plaque.[26-28] Plaques were matched between MSCT and VH IVUS as previously described.[29]

Statistical analysis

For comparisons, the patient population was divided based on gender (men versus women) and age (younger (<65 years old) patients versus older (≥65 years old) patients).

First, gender-specific characteristics of coronary atherosclerosis were evaluated in the entire patient population by comparing observations between all men and women. Secondly, age-related differences between men and women were evaluated. For this purpose, the 2 patient populations (men versus women) were further divided into younger (<65 years old) and older (≥65 years old) patients.

Categorical variables are expressed as numbers (percentages) and compared between groups with Chi-square test or Fisher's exact test. When normally distributed, continuous variables are expressed as means (standard deviation) and compared with t-test for independent samples. When not normally distributed, continuous variables are expressed as medians (interquartile range) and compared with the non-parametric Mann-Whitney test. All analyses were 2-tailed.

To minimize the effects of baseline patient characteristics, the correlation between the characteristics of coronary atherosclerosis and patient age and gender was evaluated by multivariable linear regression analysis. The analysis was performed in the 2 age groups. To determine the variables for inclusion in the final multivariable model, unpaired t-test was performed for each of the variables. Variables showing a difference in relation to the dependent variable (number of plaques per patient on MSCT, calcium score on MSCT, plaque burden on gray-scale IVUS and the arc of calcium on gray-scale IVUS) at the significance level of $p \leq 0.2$ were included in the final model.

P-values <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS software (version 14.0, SPSS Inc, Chicago, Ill, USA).

Results

Baseline clinical characteristics of the entire patient population are provided in Table 1. Of 93 patients, 59 (63%) were men and 34 (37%) were women.

IVUS examination was available in 208 (71%) of 279 vessels of 93 patients (129 (62%) vessels in men and 79 (38%) vessels in women). VH IVUS examination was available in a subpopulation of 43 (46%) patients (23 (54%) men and 20 (46%) women). The characteristics of this study subpopulation (patients with VH IVUS) were identical to the general patient population, whereas no differences in CAD risk factors and use of cardiovascular medication were observed between men and women. In total, 70 vessels were available for VH IVUS analysis (37 (53%) vessels in men and 33 (47%) vessels in women).

Table 1. Patient characteristics

Patient characteristic	Men (n=59)	Women (n=34)	P-value
Age	61±9	64±8	0.2
Body mass index	27±4	26±4	0.3
CAD risk factors			
Obesity	18 (31%)	8 (24%)	0.6
Hypercholesterolemia	46 (78%)	26 (77%)	0.9
Hypertension	30 (51%)	24 (71%)	0.06
Diabetes	11 (19%)	4 (12%)	0.4
Family history of CAD	23 (39%)	20 (59%)	0.07
Smoking	27 (46%)	17 (50%)	0.7
Previous CAD			
Previous MI	10 (17%)	5 (15%)	0.8
Previous PCI	12 (20%)	8 (24%)	0.7
Medications			
Aspirin	34 (58%)	21 (62%)	0.7
Statins	38 (64%)	24 (71%)	0.5

Data are mean±SD or n (%).

CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Gender-specific differences in coronary atherosclerosis in the entire patient population

Geometrical characteristics (plaque extent)

MSCT. MSCT coronary angiograms were of diagnostic quality in all patients.

Coronary plaques were more prevalent in men (6.7±3.8 versus 4.0±3.0 in women, p=0.001). This observation was related to a higher prevalence of obstructive plaques (2.0±2.2 in men versus 0.7±1.1 in women, p=0.002), as well as non-obstructive plaques (4.7±3.1 in men versus 3.4±2.8 in women, p=0.04).

Gray scale IVUS. A larger plaque burden was observed in men (45.7±11.4% versus 36.3±11.6% in women, p<0.001). The percentage of IVUS frames with plaque was also higher in men (87.8±19.9% versus 70.2±28.3% in women, p<0.001). In addition, a higher mean remodeling index was observed in men (1.04±0.1 versus 0.99±0.1 in women, p=0.01). Consequently, positive remodeling was more prevalent in men as compared with women (40 (31%) versus 12 (15%) respectively, p=0.02).

Compositional characteristics

MSCT. The median coronary calcium score in men was 256.0 (interquartile range 43.5-706.5) versus 72.0 (interquartile range 2.3-155.8) in women (p=0.003). In line with this observation, the number of calcified plaques on MSCT coronary angiography tended to be higher in men although no statistical significance was reached (2.7±3.5 in men versus 1.7±1.9 in women, p=0.1). Nevertheless, men had significantly more mixed plaques (2.8±3.1) as compared with women (1.3±1.5), p=0.01). Interestingly, the number of non-calcified plaques was identical in men and women (1.3±1.8 versus 1.0±1.3 respectively, p=0.5).

Gray-scale and VH IVUS. The arc of coronary calcium on gray-scale IVUS was larger in men (94.4±88.5 degrees versus 63.6±68.1 degrees in women, p=0.02).

On VH IVUS, the amount of fibrotic tissue was less in the plaques of men (53.6±7.4% versus 57.5±8.0% in the plaques of women, p=0.008). No differences were observed in the amount of fibro-fatty tissue (28.5±12.2% in men versus 25.5±10.4% in women, p=0.2), necrotic core (11.1±6.2% in men versus 10.7±5.9% in women, p=0.7) and dense calcium (6.9±6.3% in men versus 6.3±4.8% in women, p=0.6).

Likewise, no differences were observed in the prevalence of plaque types as determined on visual assessment: pathological intimal thickening was observed in 10 (16%) plaques in men versus 9 (18%) plaques in women (p=0.7), fibroatheroma was observed in 27 (42%) plaques in men versus 20 (40%) plaques in women (p=0.8), thin cap fibroatheroma was observed in 13 (20%) plaques in men versus 6 (12%) in women (p=0.2) and fibrocalcific plaque was observed in 14 (22%) plaques in men versus 15 (30%) plaques in women (p=0.3).

Gender-specific differences in coronary atherosclerosis in younger (<65 years old) patients

In total, 55 (59% of the total population) patients were <65 years old (39 (71%) men and 16 (29%) women). The mean age was 56±5 years in men and 57±5 years in women (p=0.4). No differences in the distribution of CAD risk factors, history of CAD and use of cardiovascular medication were observed between men and women.

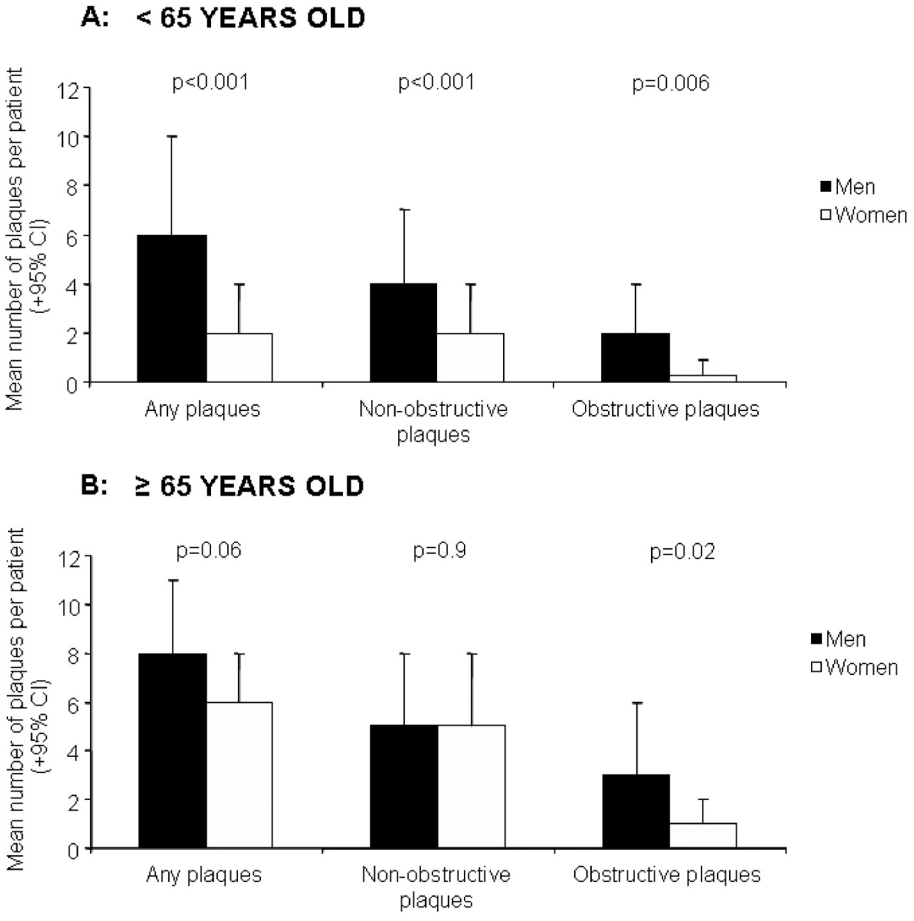

Figure 1. Coronary plaque extent on MSCT versus age and gender.
(A) Younger (<65 years old) patients: a higher prevalence of both non-obstructive and obstructive plaques was observed in men as compared with women. (B) Older (≥65 years old) patients: the number of non-obstructive plaques was identical in both genders, whereas more obstructive plaques were observed in men.

Geometrical characteristics (plaque extent)

MSCT. Geometrical characteristics of coronary atherosclerosis on MSCT in younger patients are presented in Figure 1. The number of coronary plaques was higher in men as compared with women. Both the numbers of non-obstructive and obstructive plaques were higher in men.

Table 2. Geometrical and compositional characteristics of coronary atherosclerosis on gray-scale and VH IVUS in younger (<65 years old) patients

Characteristics	Men	Women	P-value
Plaque extent and composition, gray-scale IVUS	n=90 vessels	n=37 vessels	
Vessel length (cm)	7.0±5.5	7.4±3.8	0.7
EEM area (mm^2)	16.2±8.5	12.2±3.8	0.008
Lumen area (mm^2)	8.8±4.5	8.9±3.2	1.0
Plaque burden (%)	44.8±12.3	27.9±7.9	<0.001
% abnormal frames	85.9±21.4	53.0±26.8	<0.001
Plaque volume in most diseased 10 mm	100.0±41.9	54.9±24.3	<0.001
Plaque volume in least diseased 10 mm	42.1±29.1	18.9±13.2	<0.001
Remodeling index	1.03±0.1	0.99±0.1	0.06
Positive remodeling (n(%))	27 (31%)	6 (16%)	0.1
Largest arc of calcium (degrees)	91.7±93.5	25.7±51.0	<0.001
Plaque composition, VH IVUS			
Lesion length (mm)	24.6±16.8	30.9±17.5	0.3
% fibrotic	51.1±5.1	59.1±8.7	0.001
% fibro-fatty	27.0±11.5	26.7±10.2	0.9
% necrotic core	12.8±6.8	8.5±4.1	0.04
% dense calcium	9.1±7.8	5.7±3.7	0.1
Pathologic intimal thickening	2 (7%)	3 (23%)	0.2
Fibroatheroma	8 (28%)	5 (39%)	0.5
Thin cap fibroatheroma	9 (31%)	0 (0%)	0.04
Fibrocalcific	10 (34%)	5 (38%)	1.0

Data are mean±SD or n (%).

EEM, external elastic membrane; IVUS, intravascular ultrasound; VH IVUS, virtual histology intravascular ultrasound.

Gray-scale IVUS. In total, 127 vessels were available for analysis (90 vessels in men and 37 vessels in women).

Geometrical characteristics of coronary atherosclerosis on gray-scale IVUS in younger patients are presented in Table 2. Coronary artery diameter was larger in men as compared with women. In addition, coronary plaque burden was larger in men in the entire vessel as well as in both the most and the least diseased coronary artery segments. A trend towards a higher prevalence of positive remodeling was observed in men.

Compositional plaque characteristics

MSCT. The median coronary calcium score in men was 216.0 (interquartile range 4.0-714.0) versus 3.5 (interquartile range 0-109.0) in women (p=0.003). Compositional characteristics of coronary atherosclerosis on MSCT in younger patients are presented in Figure 2. A higher number of mixed plaques was observed in men as compared with women. In addition, a trend towards a higher number of calcified plaques was observed in men.

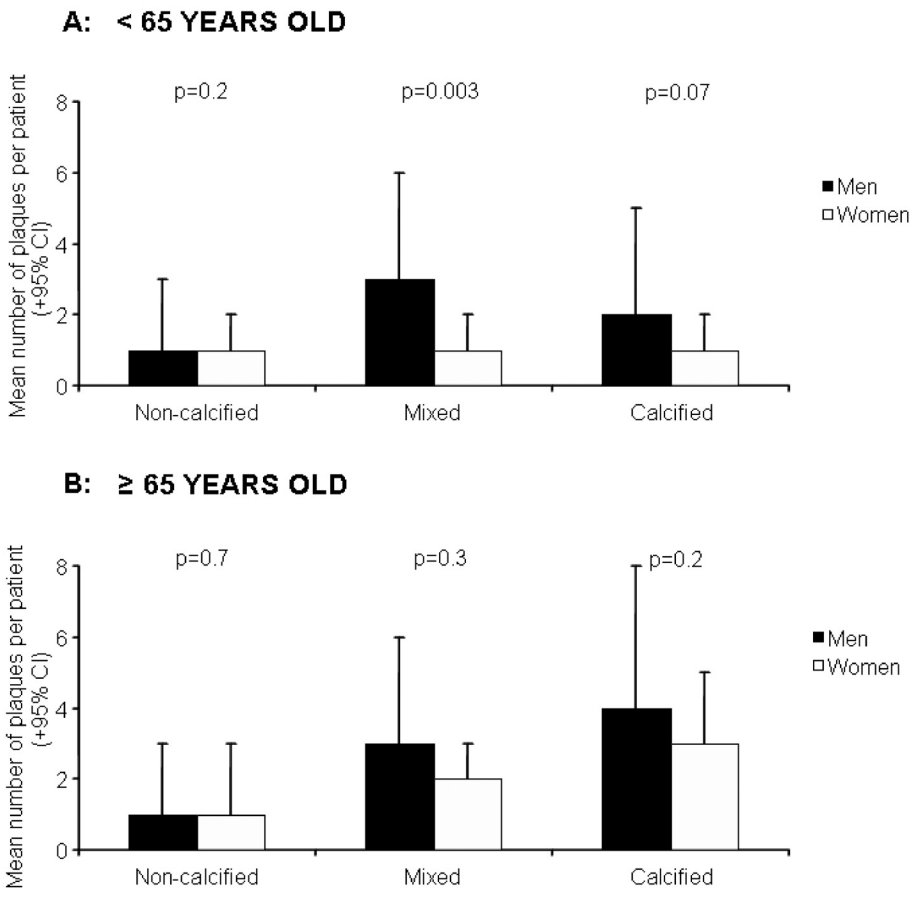

Figure 2 Coronary plaque composition on MSCT versus age and gender.
(A) Younger (<65 years old) patients: more mixed plaques and a trend towards more calcified plaques were observed in men as compared with women. (B) Older (≥65 years old) patients: no differences in coronary plaque composition were observed between men and women.

Gray-scale and VH IVUS. The arc of coronary calcium was larger in men as compared with women (Table 2).

VH IVUS was available in 32 vessels of 21 patients (21 vessels in men and 11 vessels in women). Compositional characteristics of coronary atherosclerosis on VH IVUS in younger patients are presented in Table 2. The plaques in the female population contained more fibrotic tissue, whereas more necrotic core was observed in the plaques of male patients. Thin cap fibroatheroma were observed exclusively in plaques of male patients.

Gender-specific differences in coronary atherosclerosis in older (≥65 years old) patients

In total, 38 (41% of the total population) patients were ≥65 years old (20 (53%) men and 18 (47%) women). The mean age was 72±4 years in men and 70±4 years in women (p=0.2). No differences in the distribution of CAD risk factors, history of CAD and use of cardiovascular medication were observed between men and women.

Geometrical characteristics (plaque extent)

MSCT. Geometrical characteristics of coronary atherosclerosis on MSCT in older patients are presented in Figure 1. No gender based differences were observed in the prevalence of any and non-obstructive plaques. Nevertheless, obstructive plaques were still more frequently present in the male population.

Gray-scale IVUS. In total, 81 vessels were available for analysis (39 vessels in men and 42 vessels in women).

Geometrical characteristics of coronary atherosclerosis on gray-scale IVUS in older patients are presented in Table 3. Similar to younger patients (<65 years old), coronary artery diameter remained larger in men as compared with women. Nevertheless, diffuse coronary atherosclerosis was observed in both men and women, resulting in the absence of differences of plaque burden and percentage of IVUS frames with plaque. In addition, no differences in the measures of coronary artery remodeling were observed. However, more plaque was observed in the most diseased 10 mm of the vessel in men as compared with women.

Table 3. Geometrical and compositional characteristics of coronary atherosclerosis on gray-scale and VH IVUS in older (≥65 years old) patients

Characteristics	Men	Women	P-value
Plaque extent and composition, gray-scale IVUS	n=39 vessels	n=42 vessels	
Vessel length (cm)	7.8±3.5	9.8±10.6	0.3
EEM area (mm^2)	15.3±4.8	12.6±4.6	0.009
Lumen area (mm^2)	7.9±2.6	6.9±2.2	0.07
Plaque burden (%)	47.6±9.1	43.8±8.9	0.06
% abnormal frames	92.1±15.4	85.3±19.8	0.09
Plaque volume in most diseased 10 mm	103.4±41.8	85.4±34.3	0.04
Plaque volume in least diseased 10 mm	39.7±23.1	35.6±27.9	0.5
Remodeling index	1.05±0.2	0.99±0.1	0.1
Positive remodeling (n(%))	12 (31%)	4(14%)	0.2
Largest arc of calcium (degrees)	100.1±77.7	104.1±60.8	0.8
Plaque composition, VH IVUS			
Lesion length (mm)	26.6±18.3	27.4±14.1	0.8
% fibrotic	55.7±8.3	57.0±7.8	0.5
% fibro-fatty	29.7±12.9	25.0±10.6	0.1
% necrotic core	9.6±5.3	11.4±6.2	0.2
% dense calcium	5.0±4.0	6.6±5.2	0.2
Pathologic intimal thickening	8 (23%)	6 (16%)	0.5
Fibroatheroma	19 (54%)	15 (41%)	0.2
Thin cap fibroatheroma	4 (11%)	6 (16%)	0.7
Fibrocalcific	4 (11%)	10 (27%)	0.1

Data are mean±SD or n (%).

EEM, external elastic membrane; IVUS, intravascular ultrasound; VH IVUS, virtual histology intravascular ultrasound.

Compositional plaque characteristics

MSCT. The average coronary calcium score in older men was 387.0 (interquartile range 29.0-704.0) versus 114.5 (interquartile range 36.0-363.25) in older women (p=0.03). Compositional characteristics of coronary atherosclerosis on MSCT in older patients are presented in Figure 2. No differences in plaque composition were observed between men and women.

Gray-scale and VH IVUS. The arc of calcium as measured on gray-scale IVUS was identical in the plaques of both genders (Table 3).

VH IVUS was available in 38 vessels (16 vessels in men and 22 vessels in women). Compositional characteristics of coronary atherosclerosis on VH IVUS in older patients are presented in Table 3. No differences in plaque composition were observed between 2 genders.

Progression of coronary calcification in relation to age and gender

The development of coronary calcification with increasing age is depicted in Figure 3. As can be derived from Figure 3, more extensive calcification was observed in men. However, progression of coronary calcification, as reflected by the coronary calcium score as well as the arc of calcium, was substantially more pronounced after the age of 65 years old in women as compared with men.

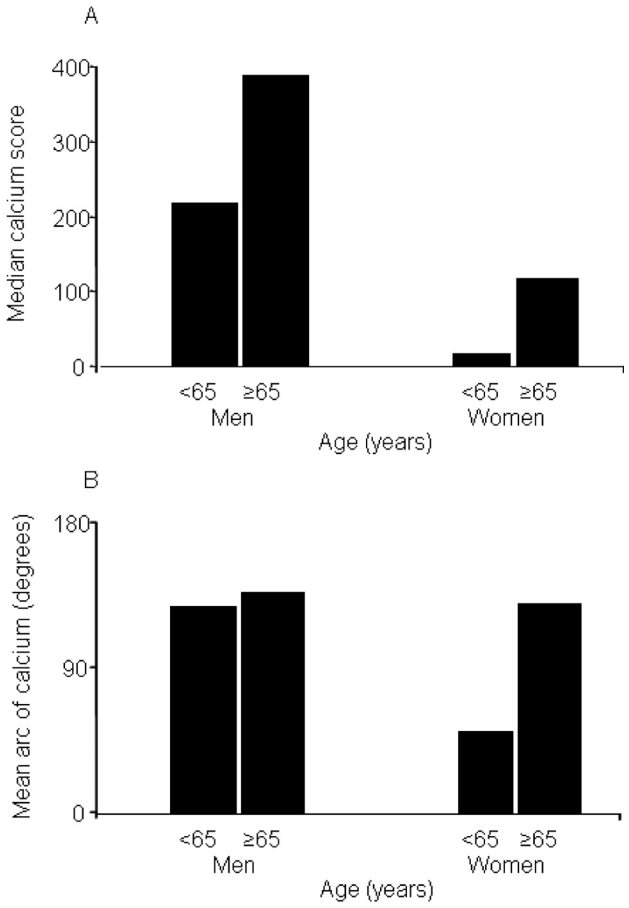

Figure 3. The progression of coronary calcification in relation to age and gender.
(A) Coronary calcium score on MSCT: a higher calcium score was observed in men. The progression of coronary calcification was more prominent after the age of 65 years old in women as compared with men. (B) The arc of calcium on gray-scale IVUS: similar pattern of progression of coronary calcification was observed on gray-scale IVUS.

Correlation between characteristics of coronary atherosclerosis, age and gender

Finally, the results of multivariable regression analysis evaluating the correlation between variables of coronary atherosclerosis and baseline patient characteristics are presented in Tables 4 and 5. As can be derived from Table 4, male gender was correlated with the measures of coronary plaque extent both on MSCT and on gray-scale IVUS in younger (<65 years old) patients. Nevertheless, this relationship was lost when the analysis was performed in the older (≥65 years old) patient group.

Table 4. Correlation between the geometrical characteristics of coronary atherosclerosis and baseline patient characteristics: multivariable regression analysis

Predictors	β coefficient (95% CI)	P-value
Nr of plaques per patient on MSCT, younger (<65 years old) patients		
Male gender	3.7 (1.7-5.7)	<0.001
Previous CAD	2.7 (0.5-4.9)	0.02
Hypercholesterolemia	-0.2 (-2.5-2.0)	0.8
Statins	1.1 (-0.9-3.1)	0.3
Nr of plaques per patient on MSCT, older (≥65 years old) patients		
Male gender	1.9 (-0.2-4.0)	0.08
Diabetes	2.4 (-0.9-5.8)	0.1
Hypertension	-0.2 (-2.5-2.1)	0.9
Plaque burden on gray-scale IVUS, younger (<65 years old) patients		
Male gender	15.0 (8.7-21.3)	<0.001
Previous CAD	2.7 (-4.3-9.7)	0.4
Smoking	-3.9 (-9.6-1.9)	0.2
Statins	3.9 (-2.2-10.0)	0.2
Plaque burden on gray-scale IVUS, older (≥65 years old) patients		
Male gender	3.0 (-2.8-8.9)	0.3
Hypercholesterolemia	-2.9 (-10.6-4.7)	0.4
Hypertension	-4.2 (-10.8-2.3)	0.2

CAD, coronary artery disease; CI, confidence intervals; IVUS, intravascular ultrasound; MSCT, multi-slice computed tomography.

Similar observations were obtained with regard to plaque composition. The coronary calcium score on MSCT and the arc of calcium on gray-scale IVUS were correlated with male gender in younger patients. No correlation between calcified lesions and gender was observed in older patients (Table 5).

Table 5. Correlation between compositional characteristics of coronary atherosclerosis and baseline patient characteristics: multivariable regression analysis

Predictors	β coefficient (95% CI)	P-value
Total calcium score on MSCT*, younger (<65 years old) patients		
Male gender	0.9 (0.2-1.6)	0.009
Smoking	-0.4 (-1.1-0.2)	0.2
Total calcium score on MSCT*, older (≥65 years old) patients		
Male gender	0.3 (-0.2-0.8)	0.3
Obesity	0.4 (-0.1-0.9)	0.1
Hypertension	-0.3 (-0.9-0.2)	0.2
Statins	-0.2 (-0.8-0.4)	0.5
The arc of calcium on gray-scale IVUS, younger (<65 years old) patients		
Male gender	66.8 (1.3-132.2)	0.04
Obesity	28.4 (-40.2-97.0)	0.4
Hypertension	44.2 (-14.5-102.9)	0.1
Smoking	-44.6 (-102.5-13.3)	0.1
The arc of calcium on gray-scale IVUS, older (≥65 years old) patients		
Male gender	26.8 (-9.4-63.0)	0.1
Diabetes	136.9 (74.1-199.6)	<0.001
Hypercholesterolemia	75.0 (12.5-137.4)	0.02
Statins	1.6 (-52.7-55.8)	1.0

* log10 transformation of the total calcium score.

CAD, coronary artery disease; CI, confidence intervals; IVUS, intravascular ultrasound; MSCT, multi-slice computed tomography.

Discussion

The findings of the study can be summarized as follows. More extensive atherosclerosis and more advanced calcified lesions were observed in men on MSCT as compared with women. Conversely, in women atherosclerosis tended to be non-obstructive with a relatively larger contribution of non-calcified plaque. The findings were confirmed on invasive gray-scale and VH IVUS. Comparison of the observations with regard to age revealed that the differences of coronary plaque observations were predominantly present in younger patients. The differences in coronary plaque extent and composition were lost or minimal between the 2 genders in older patients.

Plaque extent and severity

In the present study, less coronary plaques were observed in younger (<65 year old) women as compared with younger men both on MSCT and on gray-scale IVUS. This observation is in-line with previous IVUS studies.[12] Indeed, in a recent investigation by Nicholls et al (including 251 female patients, mean age <65 years),[12] coronary plaque burden was significantly lower in women (33.9% versus 37.8% in men, $P < 0.001$). Similarly, a pathologic study of victims of accidents revealed a lower prevalence of atherosclerotic plaque with ≥40% stenosis in young women as compared with men.[30] In contrast, Kornowski et al,[31] who performed preinterventional IVUS in slightly older women (average age 66 years) and compared findings to significantly younger male population (average age 60 years), failed to show any differences in plaque burden). Similarly, the difference in plaque extent was also lost in our study when comparing patients older than 65 years. To a large extent, these observations indicate a delay in the development of CAD in premenopausal women. Nevertheless, diffuse (non-obstructive) coronary atherosclerosis was observed in women across all ages both on MSCT and on gray-scale IVUS. Moreover, whereas CAD progression in men was related with an increase in both non-obstructive and obstructive lesions coronary atherosclerosis in women progressed with age mainly due to an increase in non-obstructive plaques. In line with this observation, plaque volume in the most diseased 10 mm remained significantly higher in older men as compared with older women, whereas no differences were observed in measures reflecting the total extent of atherosclerosis, including percentage of abnormal frames. Possibly, the presence of non-obstructive atherosclerosis in the absence of evident obstructive lesions may reflect a different manifestation of CAD and should not necessarily be considered benign. Indeed, 4 years of follow-up in the Women's Ischemia Syndrome Evaluation study revealed that women with no or minimal stenoses on invasive coronary angiography still had a 9.4% risk of death or myocardial infarction.[4] It has been hypothesized that the occurrence of chest pain in women may be related to vasculopathy in the absence of obstructive CAD.[32] Importantly, the traditional diagnostic work-up based on luminography may result in under-appreciation of CAD in women and atherosclerosis imaging may be preferable. Future research is necessary to investigate possible relationship between the presence of diffuse atherosclerosis on MSCT and coronary artery dysfunction in women.

Plaque composition

In the present study, lesions in men tended to be more calcified whereas the relative contribution of non-calcified plaques to the total plaque burden was higher in women. In younger women, smaller numbers of mixed plaques and a trend for less calcified plaques were observed on MSCT as compared with men. This observation is in line with observations by Burke et al [33] who investigated the hearts of victims of sudden death. The mean calcification load was lower in women of less than 60 years old as compared with men. Similar observations were reported on calcium scoring with electron beam computed tomography.[13] Indeed, calcium is often associated with more advanced atherosclerotic lesions.[33,34] As a result, the smaller amount of calcium in younger women may reflect less progressed atherosclerosis. Indeed, in the current study more fibrotic tissue and a trend towards a higher proportion of pathological intimal thickening were observed in the plaques of younger women on VH IVUS. In contrast, in patients <65 years old thin cap fibroatheromas were exclusively observed in men while also percentage of necrotic core was significantly higher. This is in line with observations in sudden death post-mortem studies. In men as well as older women, ruptured lesions with typically a large necrotic core and disrupted fibrous cap infiltrated by macrophages and lymphocytes were frequently observed.[35] In younger women, however, a greater tendency towards erosion of lesions that are rich in fibrotic tissue but contain limited calcium has been observed.[26,33] As a result, the differences in coronary plaque calcification in younger patients may reveal particular patterns of plaque progression in 2 genders.

Of interest, coronary calcium score as detected on MSCT was still lower in older women as compared with men, whereas the number of calcium containing lesions was the same between the 2 genders. Indeed, in line with our observations a smaller coronary artery calcium load has been observed in women of all ages in previous studies with electron beam computed tomography.[13] Nevertheless, it has also been demonstrated that similar calcium load in men and women was related with worse prognosis in women.[36] The possible explanation for this phenomenon may be two-fold. First, calcium scoring does not take coronary artery size into account. A similar calcium score may actually imply a higher percentage atheroma volume in women due to smaller vessel caliber (as also observed in the present study). Secondly, the relative contribution of non-calcified atherosclerosis to total plaque burden may be higher in women.[26,33] Accordingly, non-invasive coronary angiography with MSCT may be superior to calcium scoring as it also allows detection of non-calcified plaque and thus may provide a more reliable estimate of total plaque burden.

Interestingly, as compared with men, a more pronounced increase in coronary calcifications was observed in women over the age of 65 years old both on MSCT and on gray-scale IVUS. Indeed, also pathology and other non-invasive imaging studies have shown that an initial ~10 year lag in the development of calcifications exists. However, this phenomenon disappears during the sixth and seventh decade in women.[4,13,33] As a result, initial differences between men and women in coronary plaque composition appear to converge in older patients, as also observed in the present study.

Limitations

Observations of the current study were obtained in a relatively small patient population. In general, MSCT is still associated with an elevated radiation exposure, although radiation doses are rapidly decreasing with newer acquisition protocols. Also, no dedicated algorithms that allow quantification of plaque stenosis or volume are available for MSCT at present. An important limitation of VH IVUS is the fact that the technique is relatively new and not widely available. Moreover, the current observations need confirmation in future studies including higher patient numbers.

Conclusions

Using both non-invasive and invasive plaque imaging modalities, more extensive atherosclerosis and more advanced calcified lesions were observed in men as compared with women. Comparison of the observations with regard to age revealed that these differences were predominantly present in younger patients and were lost or minimal in older patients.

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Summary and Conclusions

SUMMARY AND CONCLUSIONS

In the introduction of this thesis (**Chapter 1**) an overview of the applications of multi-slice computed tomography (MSCT) in imaging of coronary artery disease (CAD) is provided. The technical parameters, current applications as well as strengths and limitations of the technique are discussed. Finally, the outline of the thesis is provided.

Part I

The ability of MSCT to demonstrate obstructive atherosclerotic lesions in the coronary arteries was explored in the first part of the thesis. The diagnostic accuracy of non-invasive MSCT coronary angiography in the detection of obstructive coronary artery lesions (≥50% luminal narrowing) as compared with conventional coronary angiography is described in **Chapters 2** to **4**. In **Chapter 2**, the diagnostic accuracy of 64-slice MSCT in the detection of obstructive CAD using conventional coronary angiography as the gold standard was explored in 60 patients with high pre-test likelihood of CAD. In total, 99% of coronary artery segments were of sufficient image quality. The sensitivity and specificity of MSCT to demonstrate obstructive lesions on segmental level were 85% and 97%, respectively. On a patient level, sensitivity, specificity, positive and negative predictive values were 94%, 97%, 97%, and 93%, respectively. It was concluded that 64-slice MSCT enables the accurate and non-invasive evaluation of obstructive coronary artery stenoses.

In **Chapter 3**, the influence of the patient's gender on the diagnostic accuracy of 64-slice MSCT to detect obstructive coronary lesions was investigated in 51 men and 52 women with known and suspected CAD. On segmental level, 96% coronary segments were of sufficient image quality in women and 97% segments were interpretable in men. On a patient level, the sensitivity in women and men was 95% (95% CI 87%-100%) versus 100%, the specificity was 93% (95% CI 83%-100%) versus 89% (95% CI 74%-100%), respectively. Accordingly, the findings of the study confirmed the high diagnostic accuracy of 64-slice MSCT coronary angiography both in female and in male patients.

Since the accumulation of calcium in the coronary arteries is one of the most important factors which hamper the image quality of MSCT coronary angiography, the impact of coronary calcium on the diagnostic accuracy of MSCT coronary angiography was investigated in **Chapter 4**. This impact was compared between patients examined with

the previous 16-slice MSCT scanner (41 patients) and with a more recent 64-slice MSCT scanner (60 patients). MSCT scans were analyzed with invasive coronary angiography as a standard of reference. On segmental level, the percentage of false negative segments in the groups with Agatston calcium scores 0-100, 101-400 and >400 with 16-slice MSCT were 0%, 5.3%, 2.9% ($p<0.05$), other comparisons of false positive and false negative segments both with 16- and with 64-slice MSCT were not significant. The sensitivity and specificity to detect obstructive lesions on a vessel and a patient level with 16- and 64-slice MSCT were not significantly different in different calcium score groups. In conclusion, a slight impact of coronary calcium was observed on the diagnostic accuracy of 16-slice MSCT coronary angiography on segmental level with no significant impact on a vessel and a patient level. No significant impact of coronary calcium was observed on the diagnostic accuracy of 64-slice MSCT coronary angiography on segmental, vessel and patient levels.

As patients having obstructive coronary artery lesions are frequently managed with percutaneous coronary interventions with the implantation of stents, a state-of-the-art 64-slice MSCT scanner could possibly be used to non-invasively assess coronary stent patency after implantation. Accordingly, the diagnostic accuracy of 64-slice MSCT to diagnose in-stent restenosis in 50 patients was assessed in **Chapter 5**. In total, 86% stents were determined to be assessable. All significant in-stent restenoses were detected, and the absence of significant in-stent restenosis was correctly identified in all stents, resulting in sensitivity and specificity of 100%. The negative predictive value was particularly high (100%) indicating that 64-slice MSCT may be a valuable non-invasive method to exclude in-stent restenosis.

Since both exercise testing and MSCT may be used for initial detection of CAD in patients presenting with suspected CAD, a head-to-head comparison between signs of ischemia during bicycle exercise testing and coronary atherosclerosis on MSCT was performed in **Chapter 6**. In total, 201 patients underwent exercise testing, followed by 64-slice MSCT, whereas a subgroup of 63 (31%) patients also underwent conventional coronary angiography. In 178 patients with interpretable examinations, coronary calcium score was identical in patients with a positive (11 (0-343)) and a negative exercise test (18 (0-335), p=NS). The prevalence of non-obstructive CAD on MSCT was the same in 2 patients groups (36% of patients with a positive versus 38% of patients with a negative exercise test, p=NS). Although obstructive CAD was observed on MSCT in 42% of patients having a positive exercise test, obstructive lesions were also present in 27% of patients without ischemia on exercise testing. The findings were confirmed by conventional coronary

angiography. In conclusion, no correlation was observed between ischemia on exercise testing and both calcium scoring and non-obstructive CAD on MSCT. A large proportion of obstructive lesions on MSCT were not demonstrated on exercise testing. Accordingly, MSCT may provide additional information on CAD as compared with bicycle exercise testing.

Part II

The second part of this thesis focused on characterization of coronary atherosclerotic plaque extent and composition on MSCT.

In addition to demonstration of obstructive coronary artery lesions, MSCT coronary angiography can also provide data on the presence of non-obstructive plaques and to some extent on plaque composition. Accordingly, this information may potentially be used for the assessment of patient risk for future cardiovascular events. In **Chapter 7**, the prognostic value of MSCT coronary angiography was assessed in 100 patients with known or suspected CAD. Patients were followed for the occurrence of cardiovascular events (cardiac death, non-fatal myocardial infarction, unstable angina requiring hospitalization, revascularization). During a mean follow-up of 16 months, 33 events occurred in 26 patients. In patients with normal coronary arteries on MSCT, first year event rate was 0% versus 30% (24/80) in patients with any evidence of CAD on MSCT. Observed event rate was highest in the presence of obstructive lesions (63% (20/32)) and when obstructive lesions were located in the left main/left anterior descending (LAD) coronary arteries (77% (18/23)). Nonetheless, elevated event rate was also observed in patients with non-obstructive CAD (8% (4/48)). In conclusion, MSCT coronary angiography provides independent prognostic information over baseline clinical risk factors in patients with known and suspected CAD. Excellent prognosis was noted in patients with a normal MSCT.

In order to get a better impression about coronary plaque composition on MSCT, plaque observations on MSCT were compared to a more accurate invasive modality intravascular ultrasound radiofrequency data analysis (virtual histology intravascular ultrasound (VH IVUS)). In **Chapter 8**, a head-to-head comparison of plaque observations with MSCT to VH IVUS was performed. Fifty patients underwent 64-slice MSCT followed by VH IVUS. Agatston calcium score was evaluated on MSCT in coronary segments where IVUS was performed. Plaques were classified on MSCT as non-calcified, mixed and calcified. Four plaque components were identified on VH IVUS (fibrotic, fibro-fatty, necrotic core, dense calcium) as well as the presence of thin cap fibroatheroma (TCFA) in the plaques was

assessed. A moderate correlation was observed between Agatston calcium score on MSCT and calcium volume on VH IVUS (r=0.69, p<0.0001). In total, 168 coronary plaques were evaluated (48 (29%) non-calcified, 71 (42%) mixed, 49 (29%) calcified). As compared with calcified plaques, non-calcified plaques contained more fibrotic (60.90±9.21% versus 54.60±8.33%, p=0.001) and fibro-fatty tissues (28.11±13.03% versus 21.37±9.75%, p=0.006) on VH IVUS. Mixed and calcified plaques contained more dense calcium as compared with non-calcified plaques (7.61±8.94% versus 2.68±3.01%, p=0.001; 10.18±6.71% versus 2.68±3.01%, p<0.001, respectively). TCFA were most frequently observed in mixed plaques, as compared with non-calcified and calcified plaques (32%, 13%, 8%, p=0.002, respectively). It was concluded that a good correlation was observed between calcium quantification on MSCT and VH IVUS. Plaque classification on MSCT paralleled plaque composition on VH IVUS, although VH IVUS provided more precise plaque characterization. Mixed plaques on MSCT were associated with high risk features on VH IVUS.

In **Chapter 9**, the hypothesis that different coronary plaque patterns (plaque extent and composition) may be observed both on MSCT and VH IVUS in patients presenting with acute coronary syndromes (ACS) and stable CAD was tested. Twenty five patients with ACS and 25 patients with stable CAD underwent 64-slice MSCT followed by VH IVUS in 48 (96%) patients. In ACS patients, 32% of plaques were non-calcified on MSCT and 59% were mixed. In patients with stable CAD, completely calcified lesions were more prevalent (61%). On VH IVUS, the percentage of necrotic core was higher in the plaques of ACS patients (11.16±6.07% versus 9.08±4.62% in stable CAD, p=0.02). In addition, thin cap fibroatheroma were more prevalent in ACS patients (32% versus 3% in patients with stable CAD, p<0.001) and were most frequently observed in mixed plaques on MSCT. Plaque composition both on MSCT and VH IVUS was identical between culprit and non-culprit vessels of ACS patients. In conclusion, differences in plaque characterization were demonstrated between patients with ACS and stable CAD on MSCT. Plaques of ACS patients showed features of vulnerability to rupture on VH IVUS.

Type 2 diabetes is an established risk factor of CAD. Accordingly, diabetic patients have a higher risk for developing cardiovascular events. This higher risk may be related to differences in coronary plaque extent and composition. Accordingly, the influence of type 2 diabetes on coronary plaque patterns on MSCT was assessed in **Chapters 10** and **11**. In **Chapter 10**, MSCT was performed in 215 patients (40% with type 2 diabetes).

Significantly more diseased coronary artery segments were observed in diabetic patients compared with non-diabetic patients. In particular, more non-obstructive plaques were observed in the presence of type 2 diabetes. Relatively more non-calcified, calcified and less mixed plaques were observed in diabetic patients. Thus, MSCT may be used to identify differences in coronary plaque characteristics, which may be useful for patient risk stratification.

In **Chapter 11**, coronary plaque patterns were explored in diabetic patients with higher pre-test likelihood of obstructive CAD as compared with the previous study, who were referred for invasive coronary angiography in combination with IVUS. In a population of 60 patients (19 patients with type 2 diabetes), diabetic patients showed more plaques on MSCT. On gray-scale IVUS, diabetes was associated with a larger plaque burden. Concerning plaque composition, diabetes was associated with more calcified plaques on MSCT, whereas relatively more fibrocalcific plaques were observed in diabetic patients on VH IVUS. In conclusion, particular patterns of coronary atherosclerosis were identified in diabetic patients on MSCT, which were paralleled by the findings on invasive VH IVUS.

Finally, coronary plaque patterns were evaluated in 59 men and 34 women in relation to age using MSCT, gray-scale IVUS and VH IVUS in **Chapter 12**. Coronary plaque patterns were compared between men and women in 2 age groups (<65 and ≥65 years old). In younger men, more plaques were observed on MSCT as compared with younger women, whereas a larger plaque burden was observed on gray-scale IVUS. Similarly, in younger men more mixed plaques were observed on MSCT as compared with younger women, whereas a larger arc of calcium was detected on gray-scale IVUS. On VH IVUS, the prevalence of thin cap fibroatheroma was higher in younger men (31% versus 0%). No differences in plaque patterns were observed in older men and women. Thus, a more extensive atherosclerosis and more calcified lesions were observed in men as compared with women both on non-invasive MSCT and on invasive gray-scale and VH IVUS. Moreover, these differences were predominantly present in younger patients and were lost in older patients.

Conclusions

The improvement of technical parameters of MSCT scanners during the past decade has been paralleled by a rapid improvement in image quality and diagnostic accuracy of non-invasive MSCT coronary angiography. Non-invasive coronary angiography with state-of-the-art 64-slice technology allows accurate detection of obstructive coronary artery lesions as compared with conventional coronary angiography. In particular, the negative predictive value of MSCT coronary angiography is extremely high. Accordingly, the technique may be used for non-invasive exclusion of obstructive coronary artery lesions in patients presenting with suspected CAD. In addition, the diagnostic accuracy of 64-slice MSCT coronary angiography is similar in men and women. Whereas calcium accumulation was an important factor hampering image quality of coronary angiography with previous scanner generations, the influence of coronary artery calcium seems to decrease when images are acquired with 64-slice scanner. Promising results were demonstrated in imaging of coronary artery stents with 64-slice MSCT. In comparison to exercise testing (which is frequently used as a first-line test to exclude CAD), MSCT provides more detailed information on CAD.

In addition to the demonstration of obstructive coronary artery lesions, MSCT also allows detection of non-obstructive CAD, as well as characterization of coronary plaque composition. Initial observations, including comparisons with more accurate invasive techniques, suggest that MSCT may allow detection of different coronary plaque patterns in patients with different clinical presentations. Potentially, this information may be useful in the assessment of patient risk for cardiovascular events. Nevertheless, as the technique is still in its early stage of development and as the current observations on imaging of coronary atherosclerosis with MSCT are scarce, more data, including follow-up, are needed before imaging of coronary atherosclerosis with MSCT can be applied in clinical practice.

Samenvatting en conclusies

SAMENVATTING EN CONCLUSIES

In de algemene inleiding (**Hoofdstuk 1**) wordt een overzicht gegeven van de toepassing van multi-slice computed tomography (MSCT) voor de diagnostiek van coronarialijden. De technische achtergrond, het huidige gebruik van deze techniek, evenals de voor- en nadelen daarvan worden beschreven, gevolgd door een overzicht van het proefschrift.

Deel I

In het eerste deel van het proefschrift wordt de waarde van MSCT voor de opsporing van significant coronarialijden besproken. **Hoofdstukken 2-4** verkennen de diagnostische nauwkeurigheid van MSCT voor het opsporen van significante vernauwingen in de kranslagaderen (gedefineerd als ≥50% vernauwing van het lumen van het vat) in vergelijking met traditionele invasieve coronairangiografie. In **Hoofdstuk 2** is de diagnostische nauwkeurigheid van 64-slice MSCT onderzocht om significante vernauwingen te herkennen in een populatie van 60 patiënten met een hoog risico voor coronarialijden. In totaal konden 99% van de segmenten van de kranslagaderen beoordeeld worden. Op segmentniveau werd een sensitiviteit van 85% en een specificiteit van 97% aangetoond. Op patiëntniveau bedroegen de sensitiviteit en specificiteit respectievelijk 94% en 97%. De positief en negatief voorspellende waarden waren 97% en 93%. De conclusie is dat het mogelijk is om met 64-slice MSCT op een niet-invasieve wijze nauwkeurig significante coronairestenosen te beoordelen.

In **Hoofdstuk 3** is de invloed van geslacht op de diagnostische nauwkeurigheid van 64-slice MSCT onderzocht in een populatie van 52 vrouwen en 51 mannen bekend met of met een verdenking op coronarialijden. In totaal kon 96% van de segmenten van de kranslagaderen beoordeeld worden bij vrouwen en 97% bij mannen. Op patiëntniveau werd een sensitiviteit van 95% (95% CI 87%-100%) gevonden bij vrouwen ten opzichte van 100% bij mannen, terwijl de specificiteit 93% (95% CI 83%-100%) was bij vrouwen en 89% (95% CI 74%-100%) bij mannen. Er werd geen effect van geslacht waargenomen op de nauwkeurigheid van MSCT, hetgeen suggereert dat MSCT een geschikte techniek is om zowel bij mannen als bij vrouwen coronarialijden op te sporen.

De aanwezigheid van kalk in de coronairevaten wordt gezien als een van de belangrijkste factoren die de diagnostische nauwkeurigheid van MSCT negatief kan beïnvloeden. **Hoofdstuk 4** beschrijft de invloed van kalk in de kranslagaderen op de diagnostische nauwkeurigheid van 16- en 64-slice MSCT. In totaal werden 41 patiënten onderzocht

met 16-slice MSCT en 60 patiënten met een 64-slice MSCT scanner. Bij de patiënten die met 16-slice MSCT waren onderzocht, was de verdeling van fout-negatief gescoorde segmenten bij een totale calcium score van 0-100, 101-400 en >400 respectievelijk 0%, 5.3%, 2.9% ($p<0.05$). Bij de patiënten die werden onderzocht met 64-slice MSCT werd geen significant verschil gevonden in de verdeling van het aantal fout-positief en fout-negatief gescoorde segmenten. Op het niveau van het vat en op patiëntniveau werden eveneens geen aanzienlijke effecten van kalk op de diagnostische nauwkeurigheid van 16- en 64-slice MSCT waargenomen. De resultaten van dit onderzoek suggereren dat kalk in de kranslagaderen slechts een minimaal effect heeft op de diagnostische nauwkeurigheid van 16-slice MSCT en geen effect heeft op de nauwkeurigheid van 64-slice MSCT.

Bij patiënten met significant coronarialijden wordt vaak angioplastiek met stentplaatsing verricht. In **Hoofdstuk 5** is daarom de precisie van 64-slice MSCT voor het identificeren van in-stent restenose in de kransslagaderen geëvalueerd in een populatie van 50 patiënten. In de 86% beoordeelbare stents werd een hoge sensitiviteit en specificiteit bereikt. De negatief voorspellende waarde was zeer hoog (100%). Op basis van deze resultaten kan worden geconcludeerd dat 64-slice MSCT gebruikt kan worden voor het uitsluiten van in-stent restenose.

Voor de initiële diagnostiek van coronarialijden kan zowel een fietsergometrie als een niet-invasieve MSCT toegepast worden. In **Hoofdstuk 6** wordt de relatie tussen bevindingen op fietsergometrie en coronaireatherosclerose op MSCT bepaald. Bij 201 patiënten werd zowel een 64-slice MSCT als een fietsergometrie verricht. Traditionele coronaireangiografie werd in een subpopulatie van 63 (31%) patiënten uitgevoerd. De MSCT en fietsergometrie waren beoordeelbaar in 178 (89%) patiënten. Er werd geen verschil gevonden in de totale calciumscore tussen patiënten met een positieve en negatieve fietsergometrie (11 (0-343) versus (18 (0-335), p=NS). Ook de prevalentie van niet-significant coronarialijden was gelijk in beide patiëntengroepen (36% patiënten met een positieve fietsergometrie versus 38% patiënten met een negatieve fietsergometrie, p=NS). Hoewel significant coronarialijden werd aangetoond bij 42% van de patiënten met ischemie op de fietsergometrie, werden ook significante laesies opgespoord bij 27% van de patiënten zonder tekenen van ischemie. Deze bevindingen werden bevestigd door traditionele invasieve coronaireangiografie. Samenvattend werd er geen correlatie gevonden tussen tekenen van ischemie op fietsergometrie en calciumscore, evenals niet-significant coronarialijden op MSCT. Verder werd een groot aantal significante laesies op MSCT niet aangetoond met fietsergometrie. Als gevolg van deze bevindingen werd geconcludeerd dat MSCT aanvullende informatie biedt over de aanwezigheid van coronarialijden in vergelijking met fietsergometrie.

Deel II

Het tweede gedeelte van dit proefschrift beschrijft de beoordeling van de uitgebreidheid en compositie van atherosclerotische plaques in de wand van de coronairen door middel van MSCT.

Naast het beoordelen van de aanwezigheid van significante vernauwingen van het lumen van de kranslagaderen is het met MSCT ook mogelijk de aanwezigheid van niet-obstructieve plaques evenals tot op zekere hoogte de samenstelling van de opgespoorde plaques te beoordelen. Het is dan ook goed mogelijk dat deze informatie een belangrijke rol kan spelen bij risicostratificatie. **Hoofdstuk 7** beschrijft de prognostische waarde van MSCT bij 100 patiënten bekend met of met de verdenking op coronarialijden. De patiënten werden na de MSCT-scan gedurende een periode van gemiddeld 16 maanden gevolgd voor het optreden van een cardiaal eindpunt. Tijdens de follow-up werden 33 cardiale eindpunten geobserveerd bij 26 patiënten. Bij patiënten met volledig normale kranslagaderen op MSCT werd in het eerste jaar bij geen van hen een cardiaal eidpunt geobserveerd in vergelijking tot 30% (24/80) bij patiënten met aanwijzingen voor coronarialijden op MSCT. Een cardiaal eindpunt werd het meest waargenomen bij patiënten met significant coronarialijden (20/32 (63%)) en vooral bij patiënten met significant coronarialijden in de hoofdstam en de ramus descendens anterior (18/23 (77%)). Het risico voor complicaties was ook verhoogd bij patiënten met niet-significante aterosclerotische plaques op MSCT (4/48 (8%)). De resultaten uit dit hoofdstuk laten zien dat MSCT-coronaireangiografie onafhankelijk van patiëntenkarakteristieken belangrijke prognostische informatie kan verschaffen. Patiënten met een normaal MSCT-onderzoek hebben een uitstekende prognose.

Om een betere indruk te krijgen van de samenstelling van atherosclerotische plaques op MSCT werden de karakteristieken van deze plaques op MSCT vergeleken met invasieve meting van de coronairen doormiddel van “virtual histology intravascular ultrasound” (VH IVUS). **Hoofdstuk 8** beschrijft de vergelijking tussen plaquekarakteristieken op 64-slice MSCT en VH IVUS in een populatie van 50 patiënten. De calciumscore werd bepaald in de segmenten van de kranslagaderen waar VH IVUS onderzoek was verricht. De plaques op MSCT werden verdeeld in 3 groepen (1. niet-gecalcificeerde plaques, 2. plaques met een combinatie van niet-gecalcificeerd en gecalcificeerd weefsel, 3. gecalcificeerde plaques). Vier typen weefsels konden worden gedetecteerd op VH IVUS (fibreus, fibreus-adipeus, necrotisch weefsel, kalk). Naast identificatie van deze weefsels werd eveneens de aanwezigheid bepaald van “thin cap fibroatheroma” (TCFA), een plaque

type dat gepaard gaat met een verhoogd risico op plaque ruptuur. De correlatie tussen de hoeveelheid kalk gemeten met beide technieken was redelijk (r=0.69, p<0.0001). In totaal werden 48 (29%) plaques beoordeeld als niet-gecalcificeerd, 71 (42%) als een combinatie van niet-gecalcificeerd en gecalcificeerd weefsel, en 49 (29%) als gecalcificeerd. De hoeveelheid fibreus en fibreus-adipeus weefsel was groter in de niet-gecalcificeerde plaques vergeleken met gecalcificeerde plaques. Er werd meer kalk gezien in plaques met een combinatie van niet-gecalcificeerd en gecalcificeerd weefsel en in de gecalcificeerde plaques. De prevalentie van TCFA was het hoogste in plaques met een combinatie van niet-gecalcificeerd en gecalcificeerd weefsel (gemengde plaques). Er werd geconcludeerd dat er een goede correlatie was voor kwantificatie van kalk in atherosclerotische plaques tussen de niet-invasieve MSCT en de invasieve VH IVUS. Verder was er een goede overeenkomst tussen de hoeveelheid niet-gecalcificeerd weefsel bepaald op MSCT en VH IVUS. Gemengde plaques op MSCT waren geassocieerd met eigenschappen van hoog risico op VH IVUS.

In **Hoofdstuk 9** is de hypothese onderzocht dat MSCT en VH IVUS verschillen in de patronen van atherosclerotische plaques kunnen herkennen tussen patiënten met een acuut coronair syndroom (ACS) en patiënten met stabiel coronarialijden. Bij 25 patiënten met verdenking ACS en 25 patiënten met stabiel coronarialijden werd een 64-slice MSCT-onderzoek uitgevoerd gevolgd door VH IVUS bij 48 (96%). Bij patiënten met ACS werden voornamelijk niet-gecalcificeerde plaques (32%) of gemengde plaques (59%) geïdentificeerd. Daarentegen was een significant groter gedeelte van de plaques bij patiënten met stabiel coronarialijden gecalcificeerd (61%). Op VH IVUS was het percentage van necrotisch weefsel hoger in de plaques van patiënten met ACS (11.16±6.07% versus 9.08±4.62% bij patiënten met stabiel coronarialijden, p=0.02). Een groter percentage plaques met eigenschappen van TCFA werd geïdentificeerd in patiënten met ACS (32% versus 3% in patiënten met stabiel coronarialijden, p<0.001). Een vergelijking van de culpritvaten met de niet-culpritvaten bij patiënten met ACS liet bovendien zien dat ook in de niet-culpritvaten verscheidene plaques met niet-gecalcificeerd weefsel aanwezig waren. De conclusie luidt dat MSCT verschillen laat zien in de samenstelling van atherosclerotische plaques bij patiënten met ACS vergeleken met plaques bij patiënten met stabiel coronarialijden. Op VH IVUS werden in plaques van patiënten met ACS eigenschappen van onstabiele plaques waargenomen.

Diabetes mellitus type 2 is een bekende risicofactor voor het ontwikkelen van hart en vaatziekten. Het is mogelijk dat het verhoogde risico bij patiënten met diabetes gerelateerd is aan bepaalde eigenschappen van atherosclerotische plaques. In **Hoofdstukken 10 en 11** is de invloed van diabetes mellitus type 2 onderzocht op plaquekarateristieken op MSCT. In **Hoofdstuk 10** werd MSCT verricht bij een populatie van 215 patiënten (waarvan 40% met diabetes mellitus type 2). De aanwezigheid van diabetes hield verband met het totaal aantal aangetaste coronairsegmenten en het aantal niet-significant vernauwde coronairsegmenten. De hoeveelheid van zowel niet-gecalcificeerde als gecalcificeerde plaque was positief gecorreleerd met de aanwezigheid van diabetes mellitus type 2. Gemengde plaques waren minder vaak aanwezig bij patiënten met diabetes. Op basis van dit hoofdstuk werd geconcludeerd dat MSCT verschillende plaquepatronen laat zien bij patiënten met diabetes mellitus type 2. Deze informatie kan goed worden gebruikt voor risicostratificatie.

In **Hoofdstuk 11** werd MSCT verricht bij een populatie van 60 patiënten (waarvan 19 patiënten met diabetes mellitus type 2) die in vergelijking met de patiëntenpopulatie beschreven in Hoofdstuk 10 een hogere voorafkans hadden voor coronarialijden. Na MSCT-onderzoek werd traditionele invasieve coronairangografie met gray-scale IVUS verricht. Het aantal plaques op MSCT was hoger bij patiënten met diabetes mellitus type 2. Op grayscale IVUS werd bij deze patiënten een grotere hoeveelheid plaque gezien. Bij patiënten met diabetes mellitus type 2 werden op MSCT voornamelijk gecalcificeerde plaques geïdentificeerd, tevens werd een grotere hoeveelheid kalk gezien bij deze patiënten op VH IVUS. Samenvattend werden er bijzondere plaquekarakteristieken geïdentificeerd op MSCT bij patiënten met diabetes mellitus type 2, die goed correleren met bevindingen op invasieve gray-scale en VH IVUS.

In het laatste hoofdstuk van het proefschrift (**Hoofdstuk 12**) worden plaquekarakteristieken van de kranslagaderen onderzocht bij een populatie van 59 mannen en 34 vrouwen. Bij deze patiëntenpopulatie is 64-slice MSCT verricht samen met gray-scale IVUS en VH IVUS. Plaquepatronen werden vergeleken tussen mannen en vrouwen in 2 leeftijdsgroepen (<65 and ≥65 jaar). Op MSCT werden bij jonge mannen meer plaques geïdentificeerd dan bij jonge vrouwen, terwijl een grotere hoeveelheid plaque gevonden werd op gray-scale IVUS. Overeenkomstig met deze bevinding werden tevens meer gemengde plaques (een combinatie van niet-gecalcificeerd en gecalcificeerd weefsel) ontdekt bij jonge mannen, terwijl een grotere kalkboog werd gezien op gray-scale IVUS. Op VH IVUS, was

het percentage van TCFA hoger bij jonge mannen (31% versus 0% bij jonge vrouwen). Daarentegen werden geen significante verschillen gezien tussen plaquekarakteristieken bij oudere mannen en vrouwen. Op basis van de resultaten van dit hoofdstuk wordt geconcludeerd, dat met niet-invasieve MSCT, invasieve gray-scale en VH IVUS verschillen in plaquekarakteristieken ontdekt kunnen worden bij mannen en vrouwen. Opmerkelijk is het feit dat deze verschillen vooral aanwezig zijn bij jongere patiënten.

Conclusies

De nieuwe ontwikkelingen van de onlangs geïntroduceerde MSCT-techniek in de loop van het laatste decennium gingen gepaard met een snelle verbetering van de beeldkwaliteit en de diagnostische nauwkeurigheid van deze techniek. In vergelijking met invasieve coronairangiografie is aangetoond dat de recente 64-slice MSCT zeer nauwkeurig significante vernauwingen kan opsporen. Gelet op de hoge negatief voorspellende waarde wordt de techniek bijzonder waardevol voor het uitsluiten van coronarialijden op niet-invasive wijze bij patiënten met verdenking op coronarialijden. De 64-slice MSCT lijkt even nauwkeurig te zijn bij mannen en vrouwen. Hoewel de aanwezigheid van kalk in de kranslagaderen een belangrijk negatief effect had op de beeldkwaliteit van niet-invasive coronairangiografie verricht met oudere MSCT-apparaten lijkt deze invloed van kalk in minder mate aanwezig te zijn bij beeldvorming met een recente 64-slice MSCT. Veelbelovende resultaten zijn verkregen ook bij beeldvorming van patiënten die in het verleden een stentimplantatie zijn ondergaan. Daarnaast kan MSCT meer uitgebreide informatie verschaffen bij patiënten met verdenking op coronarialijden in vergelijking met een fietstest die dagelijks toegepast wordt voor het primair uitsluiten van coronarialijden.

Een belangrijk voordeel van MSCT is dat de techniek niet alleen significante vernauwingen van de kranslagaderen laat zien, maar ook de niet-significante laesies dan wel de samenstelling van atherosclerotische plaques. Initieel onderzoek, waarbij men ook gebruik heeft gemaakt van de meer nauwkeurige invasieve technieken, heeft laten zien dat MSCT verschillende plaquekarakteristieken kan onderscheiden bij verschillende klinische presentaties. Het is dan ook goed mogelijk dat deze informatie van belang kan zijn voor risicostratificatie. Omdat de techniek zich nog in een vroeg stadium van ontwikkeling bevindt en omdat de beschikbare data op dit gebied nog spaarzaam zijn, moet vervolgonderzoek uitwijzen of deze techniek in de dagelijkse praktijk toepassing verdient.

List of Publications

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Curriculum Vitae

CURRICULUM VITAE

The author of this thesis was born on April 7, 1976, in Kaunas, Lithuania. In 1994, she graduated from Kaunas J. Jablonskis secondary school in Kaunas, Lithuania. In 1994 she started studies of medicine in Kaunas University of Medicine, Kaunas, Lithuania. During her undergraduate university studies she did part of her studies at the University of Ghent, Ghent, Belgium, within the framework of EU Erasmus program. In 2000, she entered the postgraduate residency of cardiology in Kaunas Medical University Hospital, Kaunas, Lithuania. During her residency, she completed part of her clinical training in internal medicine at the University Hospital of Lille and Tourcoing, France, as well as training in clinical echocardiography at the University Hospital of Linköping, Sweden. In 2005, she received a qualification of cardiologist in Lithuania after which she was awarded a prestigious training fellowship grant from the European Society of Cardiology and the Huygens scholarship to proceed with scientific research in cardiovascular imaging with multi-slice computed tomography at the Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands (Prof. Dr. E. E. van der Wall). This fellowship was conducted under the supervision of Prof. Dr. J. J. Bax, Prof. Dr. J. W. Jukema, and Dr. J. D. Schuijf in cooperation with the Department of Radiology (Prof. Dr. A. de Roos). Starting in 2007 (and continuing to the present), the author began a clinical fellowship in interventional cardiology at the Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands, under the supervision of Prof. Dr. M. J. Schalij.